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(54) Title: QUINOLINE DERIVATIVES AS ANTAGONISTS OF LEUKOTRIENE D ₄ (57) Abstract <p>This invention relates to quinolinyl-diaryl compounds and their use as leukotriene D₄ antagonists for the treatment of hypersensitive disorders.</p>		

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QUINOLINE DERIVATIVES AS ANTAGONISTS OF
LEUKOTRIENE D₄

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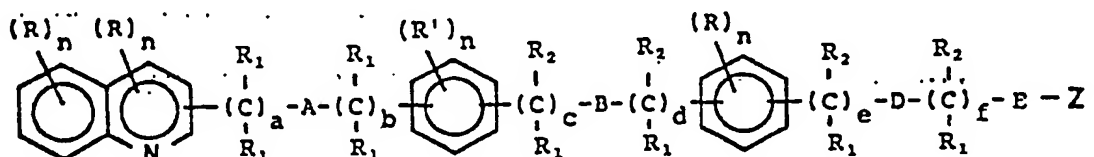
Field of Invention

This invention relates to quinolinyl phenyl compounds and their use as valuable pharmaceutical agents, particularly as lipoxygenase inhibitors and/or leukotriene antagonists possessing anti-inflammatory and anti-allergic properties.

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Summary of the Invention

This invention relates to the compounds described by the general Formula I and to therapeutic compositions comprising as active ingredient a compound of Formula I:



15

Formula I

where:

A is O or S;

B is O, S, SO, SO₂, NR₁, $-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-$, $-\overset{\text{R}_1}{\underset{\text{|}}{\text{N}}}-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-$ or $-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\overset{\text{R}_1}{\underset{\text{|}}{\text{N}}}-$;

D is O, S, NR₁, $-\overset{\text{R}_1}{\underset{\text{|}}{\text{C}}}=\overset{\text{R}_1}{\underset{\text{|}}{\text{C}}}-$ or a chemical bond;

E is a chemical bond or $-\overset{\text{R}_1}{\underset{\text{|}}{\text{C}}}=\overset{\text{R}_1}{\underset{\text{|}}{\text{C}}}-$;

20

a is 0-2;

b is 0-1;

c is 0-4;

d is 0-5;

5 e is 0-4;

f is 0-5;

n is 0-2;

R is independently hydrogen, alkyl, hydroxy, alkoxy,
10 carboxy, carbalkoxy, halo, nitro, haloalkyl, cyano or
acyl;

R' is independently hydrogen, alkyl, hydroxy, alkoxy,
halo or haloalkyl;

R₁ is independently hydrogen, alkyl or aralkyl;

R₂ is $-(CH_2)_x - X$, where x is 0-3;

15 X is hydrogen, alkyl, alkenyl, cycloalkyl, aryl
aralkyl, hydroxy, alkoxy, aralkoxy, amino, mono-and
di-alkylamino, aralkylamino, acylamino, carbamyl, carboxy,
carbalkoxy, tetrazolyl, or acylsulfonamido;

vicinal R₂ groups together may be $(CH_2)_y -$ where y is
20 1-4, thus forming a 3-6 membered ring;

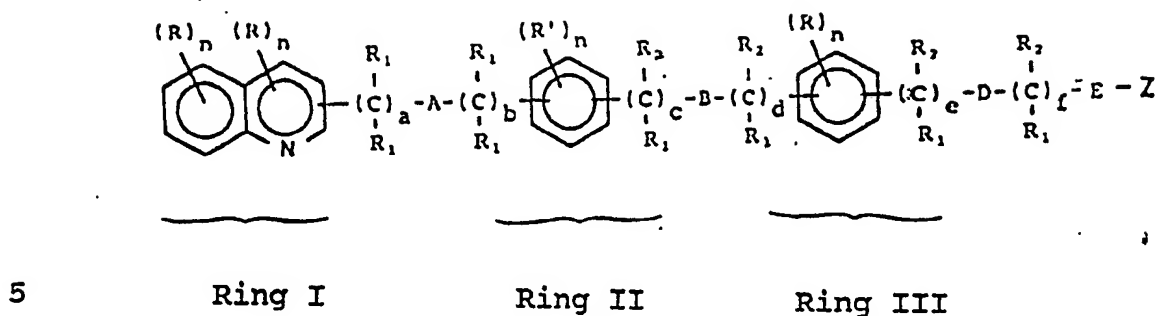
geminal R₁ and R₂ groups may together form a spiro
substituent, $-(CH_2)_z -$, where z is 2 to 5;

geminal R₁ or R₁ and R₂ groups may together form an
alkylidenyl substituent, $=CHR_1$;

25 Z is $-COOR_1$, CN, $-\overset{O}{\parallel}CNHSO_2R_3$, $-\overset{O}{\parallel}CN(R_1)_2$, $-OR_1$, tetrazolyl or
substituted tetrazolyl where the substituent may be alkyl,
carboxyalkyl or carbalkoxyalkyl;

R₃ is hydrogen, alkyl, haloalkyl, phenyl or benzyl; and
30 pharmaceutically acceptable salts thereof.

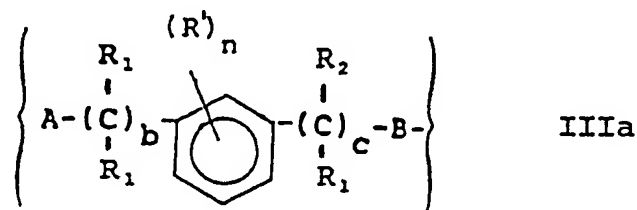
The compounds of Formula I contain at least three aromatic
rings, which may be designated as shown in Formula II below,
and for which their substitution pattern along the chain with
35 respect to each other is shown also below.



Formula II

10 The substitution pattern of the quinoline ring, that is
 Ring I, is preferably at the 2-position for extending the
 side chain. As this side chain progresses from the quinoline
 ring, the two phenyl rings, designated Ring II and Ring III
 may be substituted along the chain in the ortho, meta or para
 15 positions with respect to each other and Ring II may also be
 substituted in the ortho, meta and para positions in respect
 to the quinoline ring.

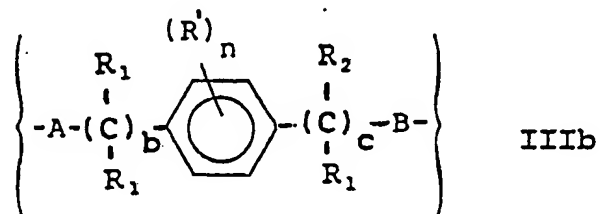
20 The preferred substitution pattern for Ring II is meta or
 para, that is:



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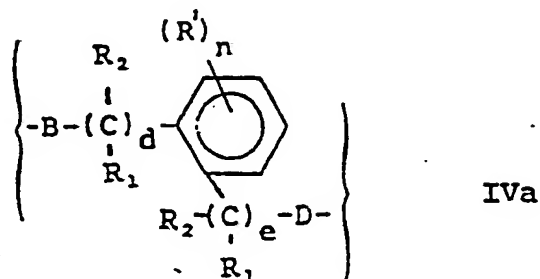
or

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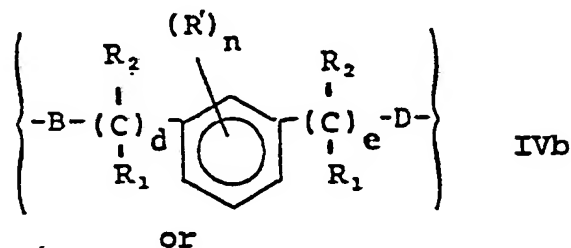


Ring III may be substituted equally in the ortho, meta or para positions, that is:

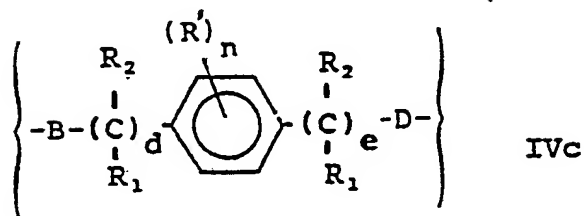
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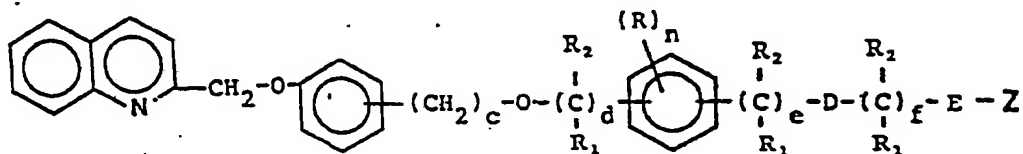


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Further preferred compounds of this invention are described by Formula V below:



25

Formula V

where $c + d = 1-3$ and $R, R_1, R_2, e, f, n, D, E$ and Z are as described above.

The more preferred compounds of Formula V are those where Z is -COOR₁; -CN; -C(=O)NHSO₂R₂, or tetrazolyl.

5 In addition, the present invention relates to the method of using these compounds as lipxygenase inhibitors and/or leukotriene antagonists possessing anti-inflammatory and anti-allergic properties.

10 As employed above and throughout the disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

15 "Alkyl", either alone or with various substituents defined herein, means a saturated aliphatic hydrocarbon, either branched or straight chained. A "loweralkyl" is preferred having about 1 to about 6 carbon atoms. Examples of alkyl include methyl, ethyl, n-propyl, isopropyl, butyl, sec-butyl, t-butyl, amyl, hexyl, etc.

20 "Alkoxy" refers to a loweralkyl-O-group.

"Alkenyl" refers to a hydrocarbon having at least one point of unsaturation and may be branched or straight chained. Preferred alkenyl groups have six or less carbon atoms and 25 include vinyl, allyl, ethynyl, isopropenyl, etc.

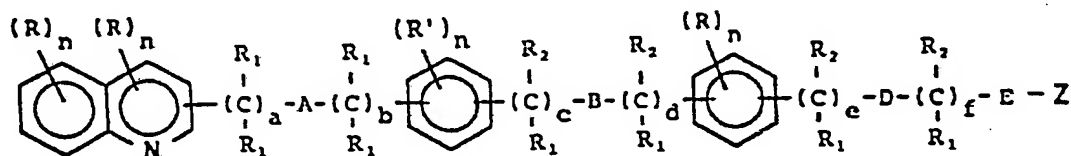
"Aralkyl" means an alkyl group substituted by an aryl radical. The preferred aralkyl groups are benzyl or phenethyl.

30 "Cycloalkyl" means a saturated monocyclic hydrocarbon ring having 3 to about 6 carbon atoms. Preferred groups include cyclopropyl, cyclohexyl, etc.

"Acyl" means an organic radical derived from an organic acid by removal of its hydroxyl group. Preferred acyl groups are groups derived from carboxylic acids. More preferred are the lower alkanoyl or benzoyl groups such as acetyl, propionyl benzoyl, etc.

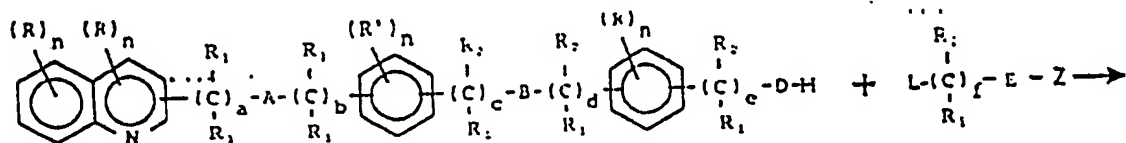
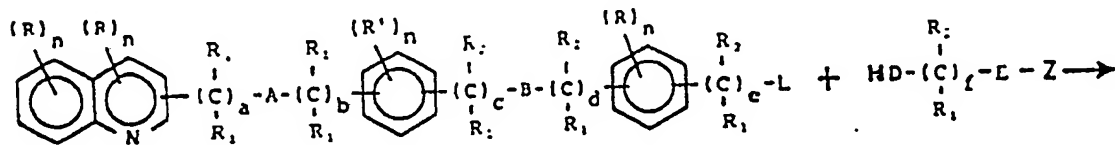
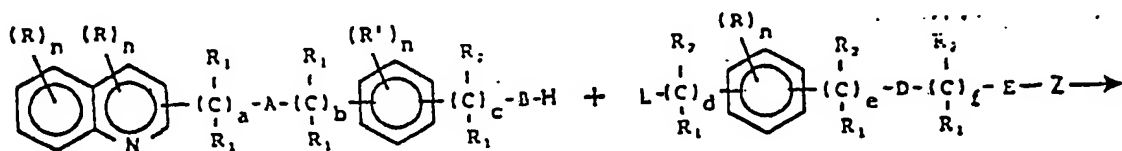
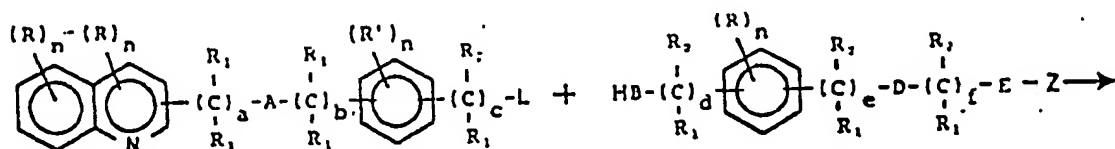
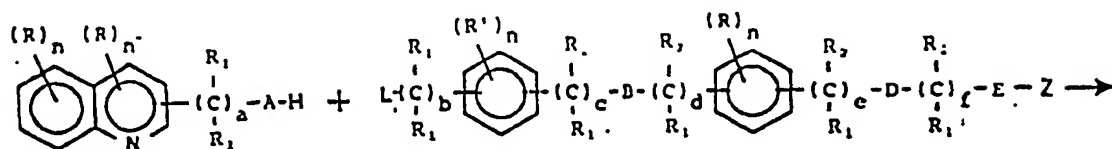
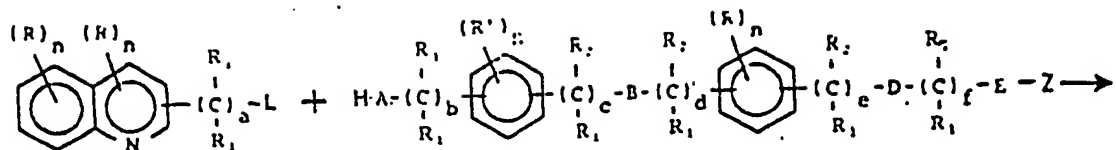
"Halo" means a halogen. Preferred halogens include, chloride, bromide and fluoride. The preferred haloalkyl group is trifluoromethyl.

The compounds of this invention may be prepared in segments as is common to a long chain molecule. Thus it is convenient to synthesize these molecules by employing condensation reactions at the A, B and D cites of the molecule. For this reason the present compounds may be prepared by art recognized procedures from known compounds or readily preparable intermediates. Exemplary general procedures are as follows and are shown where R, R', R₁ and R₂ are all hydrogen; b, d and e are 0; a, c, and f are 1; or b, c, e and f are 0 and a and d are 1. B is O, S or NR₁ and Z is -CN, -COOR₁ or tetrazolyl. Thus, in order to prepare the compound of the below formula



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the following reactions or combinations of reactions may be employed:



5 where:

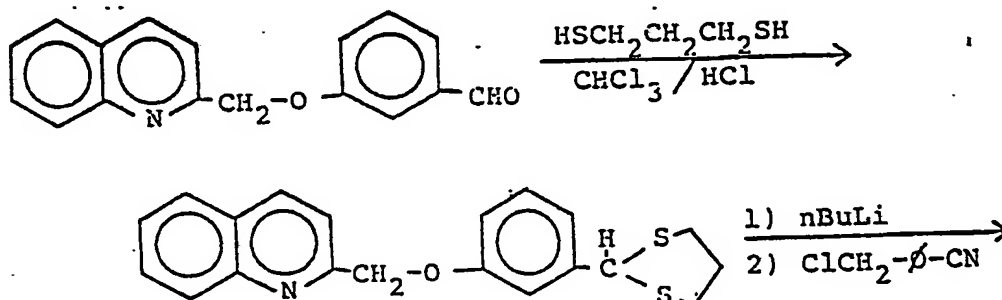
R, R', R₁, R₂, a, b, c, d, e, f, n, A, and D are as defined above; B is O or S; E is a chemical bond; Z is -CN, -COOR₁ or

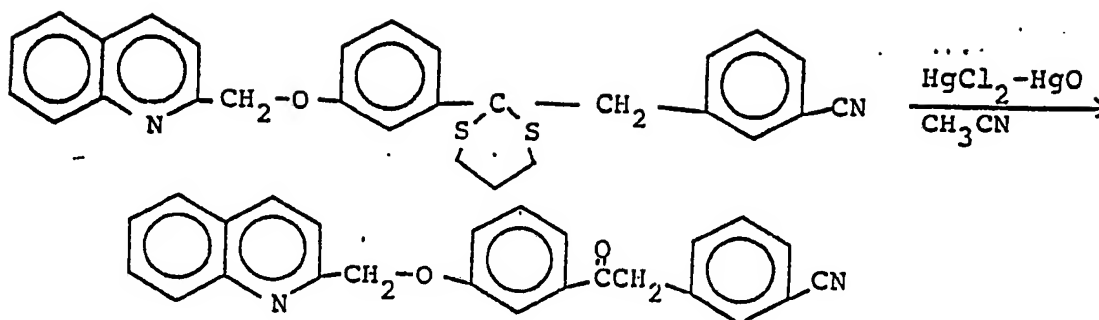
tetrazolyl, and L is a leaving group, such as halo, tosylate, or mesylate. Where B is O or S, any base normally employed to deprotonate an alcohol or thiol may be used, such as sodium hydride, sodium hydroxide, triethyl amine, sodium bicarbonate or diisopropyl/ethylamine.

Reaction temperatures are in the range of room temperature to reflux and reaction times vary from 2 to 96 hours. The reaction is usually carried out in a solvent that will dissolve both reactants and is inert to both as well. Solvents include, but are not limited to, diethyl ether, tetrahydrofuran, N,N-dimethyl formamide, dimethyl sulfoxide, dioxane and the like.

In the case where B is SO or SO then treatment of the thio compound with m-chlorobenzoic acid or sodium periodate results in the sulfinyl compound. Preparation of the sulfonyl compound may be accomplished by known procedures such as dissolving the sulfinyl compound in acetic acid and treating with 30% H₂O₂.

Those compounds where B is $\text{-}\overset{\text{O}}{\parallel}\text{C-}$ may be prepared by the following reaction sequence:





5 Condensation of the aldehyde with 1,3-propanedithiol results in the dithiane compound. This may be carried out in chloroform at reduced temperatures (-20°C) while bubbling HCl gas into the reaction mixture. The dithiane compound is then treated with N-butyl lithium in nonpolar solvent at -78°C and

10 then reacted with the substituted benzyl chloride. This results in addition of the Ring III to the molecule. The dithiane moiety is then treated with a mercuric chloride-mercuric oxide mixture to form the complex which is then split off leaving the desired compound.

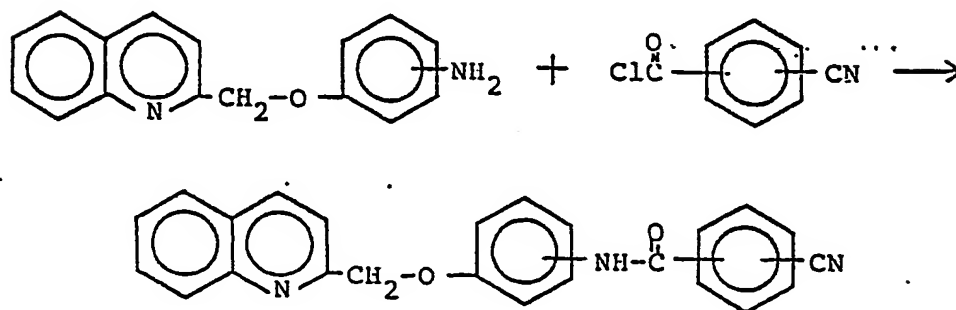
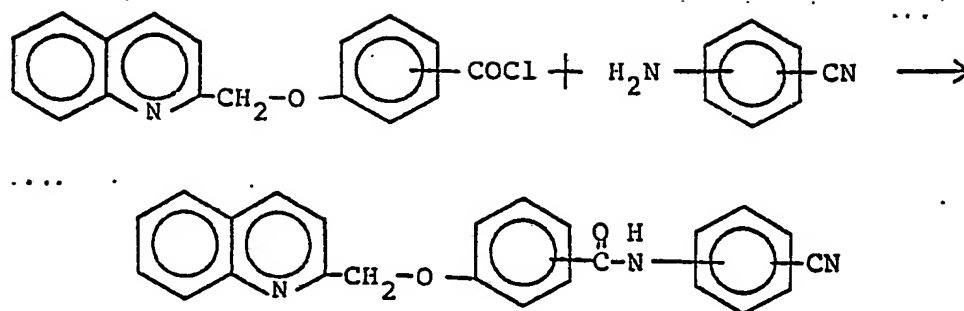
15 Those compounds where D and/or E are $\begin{array}{c} \text{R}_1 \\ | \\ -\text{C} = \text{C}- \\ | \\ \text{R}_1 \end{array}$ are prepared by reacting the appropriate aldehyde or ketone with a substituted Wittig reagent of the formula

20 $(\text{EtO})_2 - \overset{\text{O}}{\underset{\uparrow}{\text{P}}} - \underset{\text{H}}{\underset{|}{\text{(C)}}}^{\text{R}_2} - \text{Z}$, where Z is cyano or carbalkoxy.

The tetrazole may be formed from the nitrile at various stages of the synthesis by treatment with hydrazoic acid formed in situ from sodium azide and an acid.

25 When B is $\begin{array}{c} \text{R}_1 \\ | \\ -\text{N} - \text{C} - \text{O} \\ || \end{array}$ or $\begin{array}{c} \text{O} \\ || \\ -\text{C} - \text{N} - \text{R}_1 \end{array}$ then condensation of the acid halide with the appropriate aniline will give the desired compound as shown below in the following scheme.

5



- 10 The products of this invention may be obtained as racemic mixtures of their dextro and levorotatory isomers since at least one asymmetric carbon atom may be present. When two asymmetric carbon atoms are present the product may exist as a mixture of two diastereomers based on syn and anti
- 15 configurations. These diastereomers may be separated by fractional crystallization. Each diastereomer may then be resolved into dextro and levorotatory optical isomers by conventional methods.

Resolution may best be carried out in the intermediate stage where it is convenient to combine the racemic compound with an optically active compound by salt formation, ester formation, or amide formation to form two diastereomeric products. If an acid is added to an optically active base, then two diastereomeric salts are produced which possesses different properties and different solubilities and can be separated by fractional crystallization. When the salts have been completely separated by repeated crystallization, the base is split off by acid hydrolysis and the pure d and l acids are obtained.

The present compounds form salts with acids when a basic amino function is present and salts with bases when an acid function, i.e., carboxyl, is present. All such salts are useful in the isolation and/or purification of the new products. Of particular value are the pharmaceutically acceptable salts with both acids and bases. Suitable acids include, for example, hydrochloric, sulfuric, nitric, benzenesulfonic, toluenesulfonic, acetic, maleic, tartaric and the like which are pharmaceutically acceptable. Basic salts for pharmaceutical use are the Na, K, Ca and Mg salts.

Various substituents on the present new compounds, e.g., as defined in R, R₁ and R₂ can be present in the starting compounds, added to any one of the intermediates or added after formation of the final products by known methods of substitution or conversion reactions. If the substituents themselves are reactive, then the substituents can themselves be protected according to the techniques known in the art. A variety of protecting groups known in the art, may be employed. Examples of many of these possible groups may be found in "Protective Groups in Organic Synthesis" by T. W. Green, John Wiley and Sons, 1981. For example, nitro groups can be added to the aromatic ring by nitration and the nitro group converted to other groups, such as amino by reduction, and halo by diazotization of the amino group and replacement

of the diazo group. Acyl groups can be substituted onto the aryl groups by Friedel-Crafts acylation. The acyl groups can then be transformed to the corresponding alkyl groups by various methods, including the Wolff-Kishner reduction and Clemmenson reduction. Amino groups can be alkylated to form mono and dialkylamino groups; and mercapto and hydroxy groups can be alkylated to form corresponding ethers. Primary alcohols can be oxidized by oxidizing agents known in the art to form carboxylic acids or aldehydes, and secondary alcohols can be oxidized to form ketones. Thus, substitution or alteration reactions can be employed to provide a variety of substituents throughout the molecule of the starting material, intermediates, or the final product.

The compounds of the present invention have potent activity as leukotriene antagonists and as such possess therapeutic value in the treatment of inflammatory conditions and allergic responses such as anaphylaxis and asthma.

Protocol for
SRS-A (slow reacting substance of anaphylaxis) Antagonist

Leukotrienes, the products of the 5-lipoxygenase pathway of arachidonic acid metabolism, are potent contractile agents with a variety of smooth muscle preparations. Thus, it has been hypothesized that the leukotrienes contribute significantly to the pathophysiology of asthma. This protocol describes an in vitro assay used to test compounds which specifically antagonize the actions of leukotrienes.

Peripheral strips of guinea pig lungs are prepared and hung in tissue baths (Metro #ME-5505, 10 ml) according to the published procedure - (Proc. Nat'l. Acad. Sci., U.S.A. Volume 77, pp. 4354-4358, 1980). The strips are thoroughly rinsed in Assay Buffer and then connected with surgical silk thread support rods from the tissue baths. The rods are adjusted in the baths and the strips connected to the pressure transducers (Grass FT 103 or Gould US-3). The tissue baths

are aerated with 95% oxygen - 5% carbon dioxide and maintained at 37°C. The assay buffer has been made as follows: for each liter of buffer the following are added to approximately 800 ml of water distilled in glass-6.87 g NaCl, 0.4 g $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$, and 2.0 g D-glucose. Then a solution of 0.368 g $\text{CaCl}_2 \cdot \text{H}_2\text{O}$ in 100 ml glass-distilled water is slowly added to the buffer. Sufficient water is added to adjust the volume to 1 liter, and the solution is aerated with 95% oxygen - 5% carbon dioxide. Usually 10 liters of buffer are used for an experiment with 4 tissues. After the tissues have been repeatedly washed and allowed to equilibrate in the tissue bath, they are challenged with $1 \mu\text{M}$ histamine. After maximum contractions have been obtained, the tissues are washed, and allowed to relax back to baseline tension. this histamine challenge procedure is repeated at least 1 to 2 more times to obtain a repeatable control response. The average response to $1 \mu\text{M}$ histamine for each tissue is used to normalize all other challenges.

Responses of each tissue to a predetermined concentration of leukotriene are then obtained. Usually test compounds are examined initially at $30 \mu\text{M}$ on resting tension of the tissues without any added agonist or antagonist to determine if the compound has any possible intrinsic activity. The tissues are washed and the test compound is added again. Leukotriene is added after the desired pre-incubation time. The intrinsic activity of the compounds, and their effect on leukotriene-induced contractions are then recorded.

The results of this test for the compounds of the this invention indicates that these compounds are considered to be useful leukotriene antagonists.

Inhibition of (³H)-LTD₄ Binding Membranes from Guinea Pig Lung.

A. Preparation of the Crude Receptor Fraction

This procedure was adapted from Mong et al (1984). Male guinea pigs are sacrificed by decapitation and their lungs are quickly removed and placed in a beaker containing ice-cold homogenization buffer. The lungs are separated from connective tissue, minced with scissors, blotted dry and weighed. The tissue is then homogenized in 40 volumes (w/v) of homogenization buffer with a Polytron at a setting of 6 for 30 seconds. The homogenate is centrifuged at 1000 x g for 10 minutes (e.g. 3500 RPM, SS-34 Rotor). The supernate is filtered through two layers of cheese cloth and centrifuged at 30,000 x g for 30 minutes (e.g. 18,500 RPM SS-34 Rotor), after which the resulting pellet is resuspended in 20 volumes of assay buffer by hand homogenization using a Dounce homogenizer. The final pellet is resuspended in 10 volumes of assay buffer and kept at 4°C until use.

B. Binding Assay

Each assay tube (16 x 100 mm) contains the following:

490 µL Assay Buffer
10 µL Test compound or solvent
100 µL ³H-LTD₄ (ca. 17,500 DMP)
400 µL Protein preparation

Incubations are done at 25°C for 20 minutes in a shaking water bath. Reactions are started by the addition of the protein preparation. At the end of the incubation time, 4.0 ml of cold wash buffer is added to the tube. After being vortexed, the contents of the tube are immediately poured over a Whatman GF/C Filter (25 mm diameter) which is sitting in a vacuum manifold (e.g., Millipore Model No. 3025 manifold) to which a partial vacuum is applied. The filters are immediately washed with an additional 15 ml of cold buffer. The filters are transferred to 7 ml plastic scintillation vials to which 6.0 ml of appropriate

scintillation fluid (e.g., Scintiverse) is added. After being allowed to equilibrate for 4-6 hours, the radioactivity is counted with a liquid scintillation counter appropriately set for tritium.

5 The required control assay tubes include the following:

(a) Total Binding: No test compound is added; buffer is substituted.

(b) Non-Specific Binding: Non-labeled ligand is added at a concentration of $1\mu\text{M}$.

10 (c) Solvent Controls: If test compound is dissolved in a solvent, controls for both Total Binding and Non-Specific Binding containing solvent but no compounds are required.

15 The results of this test indicate that the compounds of this invention exhibit valuable properties which are useful in the treatment of inflammatory conditions and allergic responses.

20 The compounds of the present invention can be administered to a mammalian host in a variety of forms adapted to the chosen route of administration, i.e., orally, or parenterally. Parenteral administration in this respect includes administration by the following routes:
intravenous, intramuscular, subcutaneous, intraocular,
25 intrasynovial, transeptheliaily including transdermal, ophthalmic, sublingual and buccal; topically including ophthalmic, dermal, ocular, rectal and nasal inhalation via insufflation and aerosol and rectal systemic.

30 The active compound may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral
35 therapeutic administration, the active compound may be incorporated with excipient and used in the form of

ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 6% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 50 and 300 mg of active compound.

The tablets, troches, pills, capsules and the like may also contain the following: A binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and formulations.

The active compound may also be administered parenterally or intraperitoneally. Solutions of the active compound as a free base or pharmacologically acceptable salt can be

prepared in water suitably mixed with a surfactant such as hydroxypropyl-cellulose. Dispersion can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It may be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredient into a sterile vehicle

which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

The therapeutic compounds of this invention may be administer-ed to a mammal alone or in combination with pharmaceutically acceptable carriers, as noted above, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmaceutical practice.

The physician will determine the dosage of the present therapeutic agents which will be most suitable for prophylaxis or treatment and it will vary with the form of administration and the particular compound chosen, and also, it will vary with the particular patient under treatment. He will generally wish to initiate treatment with small dosages by small increments until the optimum effect under the circumstances is reached. The therapeutic dosage will generally be from 0.1 to 100 mM/day or from about 0.1 mg to about 50 mg/kg of body weight per day and higher although it may be administered in several different dosage units. Higher dosages are required for oral administration.

The compounds of the present invention may be prepared by the following representative examples.

EXAMPLE 1

3-(2-QUINOLINYLMETHYLOXY) BENZYL ALCOHOL

A mixture of 12.8 g (0.06 mol) of 2-quinolinylmethyl chloride HCl, 7.5 g (0.06 mol) of 3-hydroxybenzyl alcohol, and 18 g of potassium carbonate in 50 ml of DMF is heated at

70°C overnight. The reaction mixture is poured into water, and the precipitated product is collected, filtered and dried to give 3-(2-quinolinylmethyloxy)benzyl alcohol.

5

EXAMPLE 2

When 2-quinolinylmethyl chloride of Example 1 above is replaced by the quinoline compounds of Table I below then the corresponding product is obtained.

10

TABLE I

	2-chloromethylquinoline
	2-bromomethylquinoline
	2-(1-chloroethyl)quinoline
	2-(2-chloroethyl)quinoline
15	2-bromoethylquinoline
	3-chloromethylquinoline
	4-chloromethylquinoline
	2-(β -chloroethyl)quinoline
	2-(β -chloropropyl)quinoline
20	2-(β -chloro- β -phenethyl)quinoline
	2-chloromethyl-4-methylquinoline
	2-chloromethyl-6-methylquinoline
	2-chloromethyl-8-methylquinoline
	2-chloromethyl-6-methoxyquinoline
25	2-chloromethyl-6-nitroquinoline
	2-chloromethyl-6,8-dimethylquinoline

EXAMPLE 3

When 3-hydroxybenzyl alcohol of Example 1 above is replaced by the compounds of Table II below then the corresponding product is obtained.

30

TABLE II

	1,2-benzenediol
35	1,3-benzenediol
	1,4-benzenediol
	2-mercaptophenol

	3-mercaptophenol
	4-mercaptophenol
	1,3-dimercaptobenzene
	1,4-dimercaptobenzene
5	3-hydroxybenzyl alcohol
	3-hydroxyethylphenol
	4-hydroxybenzyl alcohol
	4-hydroxyethylphenol
	2-methylresorsinol
10	5-methylresorsinol
	5-methoxyresorsinol
	5-methyl-1,4-dihydroxybenzene
	3-(N-acetylamino)phenol
	3-(N-acetylamino)benzyl alcohol
15	2-hydroxy- α -methylbenzyl alcohol
	2-hydroxy- α -ethylbenzyl alcohol
	2-hydroxy- α -propylbenzyl alcohol
	3-hydroxy- α -methylbenzyl alcohol
	3-hydroxy- α -ethylbenzyl alcohol
20	3-hydroxy- α -propylbenzyl alcohol
	4-hydroxy- α -methylbenzyl alcohol
	4-hydroxy- α -ethylbenzyl alcohol
	4-hydroxy- α -propylbenzyl alcohol

25 EXAMPLE 4

When the compounds of Table I, Example 2 are reacted with the compounds of Table II, Example 3 under the conditions of Example 1 then corresponding products are obtained.

30 EXAMPLE 5

3-(2-QUINOLINYLMETHYLOXY) BENZYL CHLORIDE

To a stirred solution of 14.5 g of 3-(2-quinolinyl-methyloxy)benzyl alcohol in 150 ml of CHCl₃ is added
 35 dropwise 7.5 ml of thionyl chloride during 10 min. The reaction mixture is stirred for 4 hours at room temperature, and then washed with NaHCO₃ solution. The organic solution

is separated, dried, and evaporated to give 3-(2-quinolinylmethyloxy)benzyl chloride which is used without further purification in the next step.

5 EXAMPLE 6

When the compounds prepared by Examples 2-4 are used in place of 3-(2-quinolinylmethyloxy)benzyl alcohol in Example 5, then the corresponding chloride is prepared.

10 EXAMPLE 7

3-[3-(2-QUINOLINYLMETHYLOXY) BENZYLOXY] BENZONITRILE

A solution of 0.65 g (5.4 mmol) 3-hydroxybenzonitrile, 1.5 g (5.3 mmol) of 3-(2-quinolinylmethyloxy)benzyl chloride, and
15 0.75 g (5.4 mmol) of potassium carbonate in 15 ml of DMF is heated at 60°C overnight. The reaction mixture is poured into water. The precipitated product is collected on a filter and purified by dry column chromatography to give 3-[3-(2-quinolinylmethyloxy)benzyloxy]benzonitrile. (MP 86-87°C)

20 EXAMPLE 8

When 3-hydroxybenzonitrile of Example 7 above is replaced by the compounds of Table III below then the corresponding product is obtained.

25 TABLE III

	2-hydroxybenzonitrile
	3-hydroxybenzonitrile
	4-hydroxybenzonitrile
	2-cyanomethylphenol
30	3-cyanomethylphenol
	4-cyanomethylphenol
	2-cyanoethylphenol
	3-cyanoethylphenol
	4-cyanoethylphenol
35	2-cyanoethylphenol
	3-cyanopropylphenol

- 4-cyanopropylphenol
- 2-cyanopropylphenol
- 3-cyanobutylphenol
- 4-cyanobutylphenol
- 5 2-methyl-3-hydroxybenzonitrile
- 4-methyl-3-hydroxybenzonitrile
- 5-methyl-3-hydroxybenzonitrile
- 2-methyl-4-hydroxybenzonitrile
- 3-methyl-4-hydroxybenzonitrile
- 10 5-methyl-4-hydroxybenzonitrile
- 4-methoxy-3-hydroxybenzonitrile
- 3-methoxy-4-hydroxybenzonitrile
- 2-methoxy-4-hydroxybenzonitrile
- 2-methoxy-4-hydroxybenzonitrile
- 15 4-carbomethoxy-3-hydroxybenzonitrile
- 5-carbomethoxy-3-hydroxybenzonitrile
- 3-carbomethoxy-4-hydroxybenzonitrile
- 2,5-dimethyl-4-hydroxybenzonitrile
- 3-methyl-4-cyanomethylphenol
- 20 2-methyl-4-cyanomethylphenol
- 2-methyl-3-cyanomethylphenol
- 4-methyl-3-cyanomethylphenol
- 5-methyl-3-cyanomethylphenol
- 2-mercaptobenzonitrile
- 25 3-mercaptobenzonitrile
- 4-mercaptobenzonitrile
- 3-mercaptobenzylitrile
- 4-mercaptobenzylitrile
- 4-methyl-3-mercaptobenzonitrile
- 30 2-cyanomethyl-1-hydroxymethylbenzene
- 3-cyanomethyl-1-hydroxymethylbenzene
- 4-cyanomethyl-1-hydroxymethylbenzene
- 2-hydroxymethylbenzonitrile
- 3-hydroxymethylbenzonitrile
- 35 4-hydroxymethylbenzonitrile
- 3-(N-acetylamino)benzonitrile
- 4-(N-acetylamino)benzonitrile

EXAMPLE 9

When the compounds of Example 6 are used in place of 3-(2-quinolinylmethyloxy)benzyl chloride in Examples 7 and 8 then the corresponding nitriles are obtained.

EXAMPLE 105-[3-(3-(2-QUINOLINYLMETHYLOXY)BENZYLOXY)PHENYL]TETRAZOLE

10 A mixture of 1.2 g (3.28 mmol) of 3-[3-(2-quinolinylmethyloxy)benzyloxy]benzonitrile, 1.89 g (16.4 mmol) of pyridine hydrochloride, and 1.06 g (16.4 mmol) of sodium azide in 10 ml of DMF is heated at 100°C for 4 days. The reaction mixture is poured into water. The crude product
15 collected on a filter and recrystallized from ethyl acetate to give 5-[3-(3-(2-quinolinylmethyloxy)benzyloxy)-phenyl]tetrazole. (M.P. 169-172°C.)

EXAMPLE 11

20 When 4-hydroxybenzyl alcohol is used in place of 3-hydroxybenzyl alcohol in Example 1 and 4-hydroxybenzonitrile is used in place of 3-hydroxybenzonitrile in Example 7 then the product obtained is 5-[4-(4-(2-quinolinylmethyloxy)-benzyloxy)phenyl]tetrazole. (M.P. 210-213°C.)

EXAMPLE 12

25 When 4-cyanomethylphenol is used in place of 4-hydroxybenzonitrile in Example 11 then the product obtained is 5-[4-(4-(2-quinolinylmethyloxy)benzyloxy)benzyl]tetrazole. (M.P. 179-181°C.)

EXAMPLE 13

30 When the nitrile compounds of Example 9 are used in place of 3-[3-(2-quinolinylmethyloxy)benzyloxy]benzonitrile in Example 10 of corresponding tetrazole product is obtained. Representative examples of compounds obtained by this
35 invention are shown in Table IV below.

TABLE IV

	5-[3-(4-(2-quinolinylmethyloxy)benzyloxy)phenyl]tetrazole
	5-[2-(4-(2-quinolinylmethyloxy)benzyloxy)phenyl]tetrazole
5	5-[4-(3-(2-quinolinylmethyloxy)benzyloxy)phenyl]tetrazole
	5-[4-(2-(2-quinolinylmethyloxy)benzyloxy)phenyl]tetrazole
	5-[2-(3-(2-quinolinylmethyloxy)benzyloxy)phenyl]tetrazole
	5-[3-(3-(2-quinolinylmethyloxy)benzyloxy)benzyl]tetrazole
	5-[4-(3-(2-quinolinylmethyloxy)benzyloxy)benzyl]tetrazole
10	5-[3-(4-(2-quinolinylmethyloxy)benzyloxy)benzyl]tetrazole
	5-[2-(3-(2-quinolinylmethyloxy)benzyloxy)benzyl]tetrazole
	5-[4-(2-(2-quinolinylmethyloxy)benzyloxy)benzyl]tetrazole
	5-[2-(4-(2-quinolinylmethyloxy)benzyloxy)benzyl]tetrazole
	5-[2-(3-(4-(2-quinolinylmethyloxy)benzyloxy)phenyl)propyl]-
15	tetrazole
	5-[2-(3-(4-(2-quinolinylmethyloxy)benzyloxy)phenyl)butyl]-
	tetrazole
	5-[3-(3-(4-(2-quinolinylmethyloxy)benzyloxy)phenyl)butyl]-
	tetrazole
20	5-[3-(3-(2-quinolinylmethylthio)benzyloxy)phenyl]tetrazole
	5-[3-(3-(2-quinolinylmethylthio)benzylthio)phenyl]tetrazole
	5-[3-(3-(2-quinolinylmethyloxy)benzylthio)phenyl]tetrazole
	5-[4-(3-(2-quinolinylmethyloxy)benzyloxy)-3-methoxyphenyl]-
	tetrazole
25	5-[3-(3-(2-quinolinylmethyloxy)benzyloxy)-4-methoxyphenyl]-
	tetrazole
	5-[4-(4-(2-quinolinylmethyloxy)benzyloxy)-3-methoxyphenyl]-
	tetrazole
	5-[3-(4-(2-quinolinylmethyloxy)benzyloxy)-4-methoxyphenyl]-
30	tetrazole
	5-[4-(3-(2-quinolinylmethyloxy)benzyloxy)-2-methoxyphenyl]-
	tetrazole
	5-[4-(3-(2-quinolinylmethyloxy)benzyloxy)-3-carbomethoxy-
	phenyl]tetrazole
35	5-[4-(3-(2-quinolinylmethyloxy)benzyloxy)-3-methoxybenzyl]-
	tetrazole

5-[4-(4-(2-quinolinylmethyloxy)benzyloxy)-3-methoxybenzyl]-
tetrazole

5-[4-(4-(2-quinolinylmethyloxy)benzyloxy)-3-carbomethoxy-
benzyl]tetrazole

5 5-[4-(3-(2-quinolinylmethyloxy)benzyloxy)-3-carbomethoxy-
benzyl]tetrazole

5-[4-(3-(2-quinolinylmethyloxy)benzylthio)phenyl]tetrazole

5-[3-(4-(2-quinolinylmethyloxy)benzylthio)phenyl]tetrazole

5-[4-(3-(2-quinolinylmethyloxy)-N-acetyl-benzylamino)-

10 phenyl]tetrazole

5-[4-(4-(2-quinolinylmethyloxy)-N-acetyl-benzylamino)-
phenyl]tetrazole

EXAMPLE 14

15 METHYL 3-METHOXY-4-[3-(2-QUINOLINYLMETHYLOXY) BENZYLOXY]-
BENZOATE

A mixture of 3 g of 3-(2-quinolinylmethyloxy) benzyl
chloride, 1.93 g of methyl 4-hydroxy-3-methoxy benzoate, and
1.5 g of potassium carbonate in 30 ml of DMF is heated at 50°
20 overnight. The reaction mixture is poured into water, the
solid product collected on a filter and purified by dry
column chromatography to give methyl 3-methoxy-4-(3-(2-
quinolinylmethyloxy)benzyloxy)-benzoate. (M.P. 100-101°C.)

25 EXAMPLE 15

3-METHOXY-4-[3-(2-QUINOLINYLMETHYLOXY) BENZYLOXY] BENZOIC ACID

A mixture of 2.6 g of methyl 3-methoxy-4-[3-(2-quinolinyl-
methyloxy)benzyloxy]benzoate and 0.6 g of NaOH in 15 ml of
30 THF and 2 ml of H₂O are heated at 60°C overnight. The
reaction mixture is diluted with 20 ml of HO and acidified to
pH 4. The product is collected on a filter and dried to give
3-methoxy-4-(3-(2-quinolinylmethyloxy)benzyloxy)benzoic acid.
(M.P. 188-190°C.)

EXAMPLE 16

When methyl 4-hydroxy-3-methoxybenzoate is replaced in the procedure of Example 14 with the compounds of Table V, below, then the corresponding products are obtained. Representative examples of compounds prepared by this invention are shown in Table VI.

TABLE V

	methyl 2-hydroxybenzoate
10	methyl 3-hydroxybenzoate
	methyl 4-hydroxybenzoate
	methyl 4-hydroxy-3-methoxybenzoate
	methyl 3-hydroxy-4-methoxybenzoate
	methyl 4-hydroxy-2-methoxybenzoate
15	methyl 3-hydroxy-4-methoxybenzoate
	ethyl 4-hydroxy-3-ethoxybenzoate
	methyl 4-hydroxy-3-methylbenzoate
	methyl 3-hydroxy-4-methylbenzoate
	methyl 4-hydroxy-2-methylbenzoate
20	methyl 3-hydroxy-4-methylbenzoate
	methyl 4-hydroxy-2,6-dimethylbenzoate
	methyl 4-hydroxy-2,5-dimethylbenzoate
	methyl 2-hydroxyphenylacetate
	methyl 3-hydroxyphenylacetate
25	methyl 4-hydroxyphenylacetate
	methyl 4-hydroxyphenylpropionate
	methyl 4-hydroxyphenylbutyrate
	methyl 4-hydroxyphenyl-3'-methylbutyrate
	methyl 4-hydroxy-3-methylphenylacetate
30	methyl 3-hydroxy-4-methylphenylacetate
	methyl 4-hydroxy-3-methoxyphenylacetate
	methyl 3-hydroxy-4-methoxyphenylacetate
	methyl 2-hydroxymethylbenzoate
	methyl 3-hydroxymethylbenzoate
35	methyl 4-hydroxymethylbenzoate
	methyl 2-hydroxymethylphenylacetate
	methyl 3-hydroxymethylphenylacetate

methyl 4-hydroxymethylphenylacetate

3-mercaptobenzoate

4-mercaptobenzoate

3-mercaptomethylbenzoate

5 3-(N-acetylamino)benzoate

4-(N-acetylamino)benzoate

4-(N-benzylamino)benzoate

TABLE VI

- 10 4-(3-(2-quinolinylmethyloxy)benzyloxy)benzoic acid
 4-(4-(2-quinolinylmethyloxy)benzyloxy)benzoic acid
 3-(4-(2-quinolinylmethyloxy)benzyloxy)benzoic acid
 3-(3-(2-quinolinylmethyloxy)benzyloxy)benzoic acid
 2-(4-(2-quinolinylmethyloxy)benzyloxy)benzoic acid
 15 4-(3-(2-quinolinylmethyloxy)benzyloxy)phenylacetic acid
 4-(3-(2-quinolinylmethyloxy)phenoxy)benzoic acid
 4-(3-(2-quinolinylmethyloxy)benzyloxymethyl)benzoic acid
 3-methyl-4-(3-(2-quinolinylmethyloxy)benzyloxy)benzoic acid
 4-methyl-3-(3-(2-quinolinylmethyloxy)benzyloxy)benzoic acid
 20 2-methyl-4-(3-(2-quinolinylmethyloxy)benzyloxy)benzoic acid
 3-methoxy-4-(3-(2-quinolinylmethyloxy)benzyloxy)benzoic
 acid
 4-methoxy-3-(3-(2-quinolinylmethyloxy)benzyloxy)benzoic
 acid
 25 2,6-dimethyl-4-(3-(2-quinolinylmethyloxy)benzyloxy)benzoic
 acid
 4-(3-(2-quinolinylmethyloxy)benzylthio)benzoic acid
 4-(3-(2-quinolinylmethyloxy)benzylamino)benzoic acid

30 EXAMPLE 17

3-METHOXY-4-(3-(2-QUINOLINYLMETHYLOXY) BENZYLOXY) BENZOYL-N-BENZENESULFONAMIDE

- A reaction mixture of 0.73 g of 3-methoxy-4-(3-(2-
 35 quinolinyl-methyloxy)benzyloxy)benzoic acid, 0.28 g of
 benzenesulfonamide, 0.28 g of 4-dimethylpyridine, and 0.44 g
 of 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide

hydrochloride in 50 ml of CH_2Cl_2 is stirred at room temperature overnight. The solvent is removed and the residue is extracted into ethyl acetate. The organic solution is washed with water, and evaporated. The product is purified by dry column chromatography to give 3-methoxy-4-(3-(2-quinolinylmethyloxy)benzyloxy)benzoyl-N-benzenesulfonamide. (M.P. 156-158°C.)

EXAMPLE 18

When 3-methoxy-4-(3-(2-quinolinylmethyloxy)benzyloxy)benzoic acid of Example 17 is replaced by the acids of this invention such as those of Example 16, Table VI and Example 25, Table IX then the corresponding benzenesulfonamide compound is prepared.

When benzenesulfonamide is replaced in the above Examples by a sulfonamide of the formula $\text{NH}_2\text{SO}_2\text{R}_3$ or an amine of the formula $\text{HN}(\text{R}_1)_2$, then the corresponding product is obtained.

EXAMPLE 19

METHYL 3-(3-(2-QUINOLINYLMETHYLOXY)PHENOXYMETHYL) BENZOATE

A mixture of 3-(2-quinolinylmethyloxy)phenol (2.51 g, 0.01 mol), 1.85 g (0.01 mol) of methyl 3-chloromethyl benzoate, and 1.5 g of potassium carbonate in 30 ml of DMF is heated at 50°C overnight. The reaction mixture is poured into water, extracted with ethyl acetate and the organic solution separated, dried and evaporated to dryness. Recrystallization from ethyl acetate gives methyl 3-(3-(2-quinolinylmethyloxy)phenoxyethyl)benzoate. (M.P. 93-94°C.)

EXAMPLE 20

A mixture of 1.6 g of methyl 3-(3-(2-quinolinylmethyloxy)phenoxyethyl)benzoate and 0.5 g of NaOH in 20 ml of THF and 5 ml of H_2O is heated at 50°C overnight. The reaction mixture is acidified to pH 4 by 1N HCl solution, filtered and

dried to give 3-(3-(2-quinolinylmethoxy)phoxymethyl)-benzoic acid. (M.P. 149-151°C.)

EXAMPLE 21

5 When the procedures of Examples 19 and 20 are followed and methyl 3-chloromethylbenzoate is replaced by methyl 4-chloromethylbenzoate, then the product prepared is 4-(3-(2-quinolinylmethoxy)phoxymethyl)benzoic acid. (MP 190-191°C.)

EXAMPLE 22

10 When the procedures of Examples 19 and 20 are followed and methyl 3-chloromethylbenzoate is replaced by methyl 3-methoxy-4-chloromethylbenzoate then the product prepared is 3-methoxy-4-(3-(2-quinolinylmethoxy)phoxymethyl)benzoic acid. (M.P. 208-210°C.)

EXAMPLE 23

20 When the procedure of Example 19 is followed and the compounds of Table VII below are used in place of methyl 3-chloromethylbenzoate then the corresponding product is obtained.

TABLE VII

	ethyl 2-chloromethylbenzoate
25	ethyl 3-chloromethylbenzoate
	ethyl 4-chloromethylbenzoate
	ethyl 3-chloromethylbenzoate
	methyl 4-chloromethylbenzoate
	methyl 2-methyl-5-chloromethylbenzoate
30	methyl 2-methyl-3-chloromethylbenzoate
	methyl 3-methyl-5-chloromethylbenzoate
	methyl 4-methyl-5-chloromethylbenzoate
	methyl 2-methyl-4-chloromethylbenzoate
	methyl 3-methyl-4-chloromethylbenzoate
35	methyl 2-methoxy-5-chloromethylbenzoate
	methyl 2-methoxy-3-chloromethylbenzoate
	methyl 2-methoxy-4-chloromethylbenzoate

	methyl 3-methoxy-4-chloromethylbenzoate
	methyl 3-chloromethylphenylacetate
	methyl 4-chloromethylphenylacetate
	methyl 3-chloromethylphenylpropionate
5	methyl 4-chloromethylphenylpropionate
	methyl 3-chloromethylphenylbutyrate
	methyl 4-chloromethylphenylbutyrate
	methyl 3-chloromethylphenylisopropionate
	methyl 4-chloromethylphenylisopropionate
10	methyl 3-chloromethylphenylisopropionate
	methyl 4-chloromethylphenylisobutyrate

EXAMPLE 24

When the procedure of Example 19 is followed and the compound of Table VIII below are used in place of 3-(2-quinolinyl-methyloxy)phenol then the corresponding product is obtained.

TABLE VIII

20	3-(2-quinolinylmethyloxy)phenol
	4-(2-quinolinylmethyloxy)phenol
	3-(2-quinolinylmethylthio)phenol
	4-(2-quinolinylmethylthio)phenol
	5-methyl-3-(2-quinolinylmethyloxy)phenol
25	2-methyl-3-(2-quinolinylmethyloxy)phenol
	5-methoxy-3-(2-quinolinylmethyloxy)phenol
	2-methyl-4-(2-quinolinylmethyloxy)phenol
	2-methoxy-4-(2-quinolinylmethyloxy)phenol
	3-methoxy-4-(2-quinolinylmethyloxy)phenol
30	3-methyl-4-(2-quinolinylmethyloxy)phenol
	3-(2-quinolinylmethyloxy)phenyl mercaptan
	4-(quinolinylmethyloxy)phenyl mercaptan
	3-(2-quinolinylmethylthio)phenyl mercaptan
	4-(2-quinolinylmethylthio)phenyl mercaptan
35	N-benzyl-3-(2-quinolinylmethyloxy)phenylamine
	N-methyl-3-(2-quinolinylmethyloxy)phenylamine

N-acetyl-3-(2-quinolinylmethyloxy)phenylamine

N-acetyl-4-(2-quinolinylmethyloxy)phenylamine

EXAMPLE 25

- 5 When the procedures of Examples 19 and 20 are followed using the compounds of Table VII, Example 23 and Table VIII, Example 24, then the corresponding product is obtained. Representative examples of compounds prepared by this invention are shown in Table IX.

TABLE IX

- 10 3-(4-(2-quinolinylmethyloxy)phenoxyethyl)benzoic acid
 4-(4-(2-quinolinylmethyloxy)phenoxyethyl)benzoic acid
 2-(3-(2-quinolinylmethyloxy)phenoxyethyl)benzoic acid
 2-(4-(2-quinolinylmethyloxy)phenoxyethyl)benzoic acid
 15 2-methyl-3-(3-(2-quinolinylmethyloxy)phenoxyethyl)benzoic acid
 2-ethyl-3-(3-(2-quinolinylmethyloxy)phenoxyethyl)benzoic acid
 2-methoxy-3-(3-(2-quinolinylmethyloxy)phenoxyethyl)benzoic acid
 20 3-methyl-4-(3-(2-quinolinylmethyloxy)phenoxyethyl)benzoic acid
 2-methyl-4-(3-(2-quinolinylmethyloxy)phenoxyethyl)benzoic acid
 25 2-methoxy-4-(3-(2-quinolinylmethyloxy)phenoxyethyl)benzoic acid
 3-(3-(2-quinolinylmethyloxy)-5-methylphenoxyethyl)benzoic acid
 3-(3-(2-quinolinylmethyloxy)-5-methoxyphenoxyethyl)benzoic acid
 30 3-(4-(2-quinolinylmethyloxy)-3-methylphenoxyethyl)benzoic acid
 3-(4-(2-quinolinylmethyloxy)-2-methylphenoxyethyl)benzoic acid
 35 2-methyl-3-(3-(2-quinolinylmethyloxy)-2-methylphenoxyethyl)benzoic acid

3-(3-(2-quinolinylmethylthio)phenoxy)methyl)benzoic acid
 4-(4-(2-quinolinylmethylthio)phenoxy)methyl)benzoic acid
 3-(3-(2-quinolinylmethyloxy)phenoxy)methyl)phenylacetic acid
 3-(3-(2-quinolinylmethyloxy)phenoxy)methyl)phenylpropionic
 5 acid
 3-(3-(2-quinolinylmethyloxy)phenylthiomethyl)benzoic acid
 4-(3-(2-quinolinylmethyloxy)phenylthiomethyl)benzoic acid
 3-(4-(2-quinolinylmethyloxy)phenylthiomethyl)benzoic acid
 3-(3-(2-quinolinylmethyloxy)phenyl-N-acetylaminomethyl)-
 10 benzoic acid
 4-(4-(2-quinolinylmethyloxy)phenyl-N-acetylaminomethyl)-
 benzoic acid

EXAMPLE 26

15 4-(3-(2-QUINOLINYLMETHYLOXY) PHENOXYMETHYL) BENZONITRILE

A solution of 7.24 g (19.92 mmol) of sodium 3-(2-quinolinylmethyloxy)phenoxide pentahydrate and 4.68 g (23.90 mmol) of p-cyanobenzyl bromide in 34 ml of dry DMF is stirred at 75°C under nitrogen for 2 days. The reaction
 20 mixture is cooled to room temperature, then poured into 400 ml of 3:1 H₂O/Et₂O, shaken, and the phases separated. The aqueous layer is extracted and washed with 1:1 brine/H₂O and brine. The ether solution is dried over 1:1 Na₂SO₄/MgSO₄, filtered and concentrated. The crude product is
 25 recrystallized from 70% EtOAc/hexane to obtain 4-(3-(2-quinolinylmethyloxy)phenoxy-methyl)benzonitrile. (M.P. 112.5°C.)

EXAMPLE 275-(4-(3-(2-QUINOLINYLMETHYLOXY)PHENOXYMETHYL)PHENYL)TETRAZOLE

A slurry of 2.0 g (5.48 mmol) of 4-(3-(2-quinolinyl-
5 methyloxy)phenoxy-methyl)benzonitrile, 1.78 g (27.4 mmol) of
sodium azide, and 3.16 g (27.4 mmol) of pyridinium
hydrochloride in 12 ml of dry DMF is stirred under nitrogen
at 100°C for 20 hrs. The reaction mixture is then cooled to
room temperature and concentrated. The residue is taken up
10 on 100 ml of 1N aqueous NaOH and the solution extracted with
ether. The aqueous layer is acidified to pH 6 with 1N
aqueous HCl, and the precipitate collected, triturated with
water, filtered and lyophilized to obtain 5-(4-(3-(2-
quinolinylmethyloxy)phenoxy-methyl)phenyl)tetrazole. (M.P.
15 91°C dec.)

EXAMPLE 28

When the procedures of Examples 26 and 27 are followed and
p-cyanobenzyl bromide is replaced by o-cyanobenzyl bromide,
20 m-cyanobenzyl bromide, o-(cyanomethyl)benzyl bromide, m-
(cyanomethyl)benzyl bromide, p-(cyanomethyl)-benzyl bromide,
then the products prepared are:

5-(2-(3-(2-quinolinylmethyloxy)phenoxy-methyl)phenyl)tetrazole
25 (M.P. 166-170°C);
5-(3-(3-(2-quinolinylmethyloxy)phenoxy-methyl)phenyl)tetrazole
(M.P. 115°C dec.);
5-(2-(3-(2-quinolinylmethyloxy)phenoxy-methyl)benzyl)tetrazole
(M.P. 145.5-147°C);
30 5-(3-(3-(2-quinolinylmethyloxy)phenoxy-methyl)benzyl)tetrazole
(M.P. 161-164°C); and
5-(4-(3-(2-quinolinylmethyloxy)phenoxy-methyl)benzyl)tetrazole
(M.P. 149-152°C).

EXAMPLE 29

When the procedure of Example 26 is followed and the compounds of Table X below are used in place of p-cyanobenzyl bromide then the corresponding product is obtained.

5

TABLE X

2-methyl-4-cyanobenzyl bromide

3-methyl-4-cyanobenzyl bromide

3-methoxy-2-cyanobenzyl bromide

2-methyl-3-cyanobenzyl bromide

10 3-cyano-4-methylbenzyl bromide

4-methoxy-2-cyanobenzyl bromide

3-cyano-5-methylbenzyl bromide

2-methyl-5-cyanobenzyl bromide

2-methoxy-5-cyanobenzyl bromide

15 2-methoxy-4-cyanobenzyl bromide

2-methoxy-3-cyanobenzyl bromide

2,6-dimethyl-4-cyanobenzyl bromide

3-methoxy-4-cyanobenzyl bromide

2-methyl-6-cyanobenzyl bromide

20 o-cyanobenzyl bromide

m-cyanobenzyl bromide

p-cyanobenzyl bromide

2-cyanomethylbenzyl bromide

3-cyanomethylbenzyl bromide

25 4-cyanomethylbenzyl bromide

3-(1'-cyanoethyl)benzyl bromide

3-(2'-cyanoethyl)benzyl bromide

4-(1'-cyanoethyl)benzyl bromide

4-(2'-cyanoethyl)benzyl bromide

30 3-(1'-cyanopropyl)benzyl bromide

3-(2'-cyanopropyl)benzyl bromide

3-(3'-cyanopropyl)benzyl bromide

4-(1'-cyanopropyl)benzyl bromide

4-(2'-cyanopropyl)benzyl bromide

35 4-(3'-cyanopropyl)benzyl bromide

3-(1'-cyanobutyl)benzyl bromide

3-(2'-cyanobutyl)benzyl bromide
 3-(3'-cyanobutyl)benzyl bromide
 3-(4'-cyanobutyl)benzyl bromide
 4-(1'-cyanobutyl)benzyl bromide
 5 4-(2'-cyanobutyl)benzyl bromide
 4-(3'-cyanobutyl)benzyl bromide
 4-(4'-cyanobutyl)benzyl bromide
 3-(2'-methyl-1'-cyanobutyl)benzyl bromide
 3-(3'-methyl-1'-cyanobutyl)benzyl bromide
 10 4-(2'-methyl-1'-cyanobutyl)benzyl bromide
 4-(3'-methyl-1'-cyanobutyl)benzyl bromide

EXAMPLE 30

When the procedure of Example 26 is followed and the sodium
 15 or other appropriate salt of the alcohol or mercaptan of
 Table VIII, Example 24 is used in place of sodium 3-(2-
 quinolinylmethyloxy)-phenoxide then the corresponding product
 is obtained.

EXAMPLE 31

When the procedures of Examples 26 and 27 are followed
 using the compounds of Table X, Example 29 and the
 appropriate alcohol, thio or amino salt formed in Example 30,
 then the corresponding products are obtained. Representative
 25 examples of compounds prepared by this invention are shown in
 Table XI.

TABLE XI

5-(4-(4-(2-quinolinylmethyloxy)phenoxy)methyl)phenyl)
 30 tetrazole
 5-(3-(4-(2-quinolinylmethyloxy)phenoxy)methyl)phenyl)
 tetrazole
 5-(3-(2-(2-quinolinylmethyloxy)phenoxy)methyl)phenyl)
 tetrazole
 35 5-(2-(4-(2-quinolinylmethyloxy)phenoxy)methyl)phenyl)
 tetrazole
 5-(4-(2-(2-quinolinylmethyloxy)phenoxy)methyl)phenyl)

- tetrazole
5-(2-(2-(2-quinolinylmethyloxy)phenoxy)methyl)phenyl)
tetrazole
5-(3-(3-(2-quinolinylmethyloxy)phenoxy)methyl)phenyl)
5 tetrazole
5-(4-(3-(2-quinolinylmethyloxy)-5-methoxyphenoxy-
methyl)phenyl)tetrazole
5-(4-(3-(2-quinolinylmethyloxy)-5-methylphenoxy-
methyl)phenyl)tetrazole
10 5-(3-(4-(2-quinolinylmethyloxy)-2-methylphenoxy-
methyl)phenyl)tetrazole
5-(3-(4-(2-quinolinylmethyloxy)-2-methoxyphenoxy-
methyl)phenyl)tetrazole
5-(4-(3-(2-quinolinylmethyloxy)-2-methylphenoxy)methyl)-
15 phenyl)tetrazole
5-(4-(4-(2-quinolinylmethyloxy)-2-methylphenoxy)methyl)-
phenyl)tetrazole
5-(4-(4-(2-quinolinylmethyloxy)-3-methylphenoxy)methyl)-
phenyl)tetrazole
20 5-(4-(3-(2-quinolinylmethylthio)phenoxy)methyl)phenyl)-
tetrazole
5-(3-(3-(2-quinolinylmethylthio)phenoxy)methyl)phenyl)-
tetrazole
5-(2-(3-(2-quinolinylmethylthio)phenoxy)methyl)phenyl)-
25 tetrazole
5-(2-(4-(2-quinolinylmethyloxy)phenoxy)methyl)benzyl)-
tetrazole
5-(4-(4-(2-quinolinylmethyloxy)phenoxy)methyl)benzyl)-
tetrazole
30 5-(3-(4-(2-quinolinylmethyloxy)phenoxy)methyl)benzyl)-
tetrazole
5-(4-(3-(2-quinolinylmethyloxy)phenoxy)methyl)-
phenethyl)tetrazole
5-(3-(2-(4-(2-quinolinylmethyloxy)phenoxy)methyl)-
35 phenyl)propyl)tetrazole
5-(4-(3-(2-(2-quinolinylmethyloxy)phenoxy)methyl)-
phenyl)butyl)tetrazole

- 5-(2-(4-(3-(2-quinolinylmethyloxy)phenoxy)methyl)-phenyl)propyl)tetrazole
- 5-(3-(4-(3-(2-quinolinylmethyloxy)phenoxy)methyl)-phenyl)butyl)tetrazole
- 5 5-(4-(4-(3-(2-quinolinylmethyloxy)phenoxy)methyl)-phenyl)-3-methylbutyl)tetrazole
- 5-(4-(3-(2-quinolinylmethyloxy)phenylthiomethyl)-phenyl)tetrazole
- 5-(4-(3-(2-quinolinylmethylthio)phenylthiomethyl)-phenyl)tetrazole
- 10 5-(4-(3-(2-quinolinylmethyloxy)phenoxy)methyl)-3-methylphenyl)tetrazole
- 5-(4-(3-(2-quinolinylmethyloxy)phenoxy)methyl)-2-methylphenyl)tetrazole
- 15 5-(4-(3-(2-quinolinylmethyloxy)phenoxy)methyl)-2-methoxyphenyl)tetrazole
- 5-(4-(3-(2-quinolinylmethyloxy)phenoxy)methyl)-3-methoxyphenyl)tetrazole
- 5-(2-(4-(2-quinolinylmethyloxy)phenoxy)methyl)-3-methylphenyl)tetrazole
- 20 5-(3-(4-(2-quinolinylmethyloxy)phenoxy)methyl)-4-methoxyphenyl)tetrazole
- 5-(3-(3-(2-quinolinylmethyloxy)phenoxy)methyl)-4-methoxyphenyl)tetrazole
- 25 5-(4-(3-(2-quinolinylmethyloxy)-5-methylphenoxy-methyl)-2-methoxyphenyl)tetrazole
- 5-(4-(3-(2-quinolinylmethyloxy)-N-acetylphenylamino-methyl)phenyl)tetrazole
- 5-(4-(3-(2-quinolinylmethylthio)-N-acetylphenylamino-methyl)phenyl)tetrazole
- 30

EXAMPLE 32

- 35 5-(3-(4-(2-QUINOLINYL METHYLOXY)-PHENOXYMETHYL) PHENOXYMETHYL) TETRAZOLE

A. α -(3-hydroxymethylphenoxy)acetonitrile

A mixture of 3-hydroxymethyl phenol (0.081 mol), bromoacetonitrile (0.081 mol) and anhydrous potassium carbonate (0.081 mol) in acetone (160 ml) and dimethylformamide (20 ml) are heated at reflux for 48 hrs. The reaction mixture is filtered and evaporated. The residue is diluted with ethyl acetate (150 ml), washed with 10% aqueous sodium hydroxide solution (3x100 ml) and then with brine (3x100 ml). The ethyl acetate solution is dried (magnesium sulfate) and chromatographed using a silica gel column (ca. 100 g) and eluted with 1:1 petroleum ether: ethylacetate (2 l). The resultant oil is used directly in the next step.

B. α -(3-chloromethylphenoxy)acetonitrile

α -(3-Hydroxymethylphenoxy)acetonitrile (0.055 mol) in diethylether (150 ml) is stirred with thionyl chloride (0.060 mol) and a few drops of dimethylformamide at 40°C for 1 hr. the solution is washed with water and brine, then evaporated to give α -(3-chloromethylphenoxy)acetonitrile as a yellow oil which is used directly in the next step.

C. α -(3-(4-(2-quinolinylmethyloxy)phenoxy)methyl)phenoxy)acetonitrile

A mixture of α -(3-chloromethylphenoxy)acetonitrile (0.025 mol), sodium 4-(2-quinolinylmethyloxy)phenoxide (0.025 mol) and anhydrous potassium carbonate (.125 mol) in dimethylsulfoxide (50 ml) is stirred at ambient temperature for 18 hrs. The reaction is diluted with water (600 ml) and extracted with ethyl acetate (3x150 ml). The ethyl acetate solution is washed with water (3x100 ml) and brine (100 ml) then dried and evaporated to give α -(3-(4-(2-quinolinylmethyloxy)phenoxy)methyl)phenoxy)acetonitrile. (M.P. 110-114°C.)

D. 5-(3-(4-(2-quinolinylmethyloxy)phenoxy)methyl)-
phenoxy)methyl)tetrazole

α -(3-(4-(2-quinolinylmethyloxy)phenoxy)methyl)phenoxy)-
acetonitrile (8.12 mmol), sodium azide (24.4 mmol) and
5 ammonium chloride (24.4 mmol) in dimethylformamide (10 ml)
are heated at 115-120°C for 6 hrs. After cooling, the
reaction mixture is diluted with ethyl acetate (150 ml),
washed with water (6x100 ml) then dried and evaporated.
The residue is chromatographed on a column of silica gel
10 (360 g) and eluted with a gradient of isopropanol in
methylene chloride to give 5-(3-(4-(2-quinolinylmethyl-
oxy)phenoxy)methyl)phenoxy)methyl)tetrazole. (M.P. 131-
132°C.)

EXAMPLE 33

15 When sodium 4-(2-quinolinylmethyloxy)phenoxide of Example
32, Step C, is replaced with sodium 3-(2-quinolinylmethyl-
oxy)phenoxide, the product prepared is 5-(3-(3-(2-quinolinyl-
methyloxy)phenoxy)methyl)phenoxy)methyl)tetrazole. (M.P. 135-
137°C.)

EXAMPLE 34

20 When α -(3-hydroxymethylphenoxy)acetonitrile of Example 33,
Step B, is replaced with α -(4-hydroxymethylphenoxy)-
acetonitrile then the product prepared is 5-(4-(3-(2-
quinolinylmethyloxy)phenoxy)methyl)phenoxy)methyl)tetrazole.
25 (M.P. 154-156°C.)

EXAMPLE 35

When α -(3-hydroxymethylphenoxy)acetonitrile of Example 33,
Step B, is replaced with α -(2-hydroxymethylphenoxy)-
30 acetonitrile or α -[(2-hydroxymethyl-5-carbomethoxy)phenoxy]-
acetonitrile then the products prepared are 5-(2-(3-(2-
quinolinylmethyloxy)phenoxy)methyl)phenoxy)methyl)tetrazole
(M.P. 118-120°C) or 5-(2-(3-(2-quinolinylmethyloxy)-
phenoxy)methyl)-5-carbomethoxy-phenoxy)methyl)tetrazole.
35 (M.P. 159-162°C.)

EXAMPLE 36

When bromoacetonitrile of Example 32, Step A is replaced by the nitriles of Table XII below then the corresponding product is prepared:

5

TABLE XII

bromoacetonitrile
 α -bromo- α -methylacetonitrile
 α -bromo- β -ethylacetonitrile
 α -bromopropionitrile
10 β -bromopropionitrile
 β -bromo- β -methylpropionitrile
-bromobutyronitrile
 β -bromobutyronitrile
 α -bromobutyronitrile

15

EXAMPLE 37

When 3-hydroxymethylphenol of Example 32, Step A is replaced by the compounds of Table XIII below, then the corresponding products are prepared.

20

TABLE XIII

2-hydroxymethylphenol
3-hydroxymethylphenol
4-hydroxymethylphenol
3-mercaptobenzylalcohol
25 4-mercaptobenzylalcohol
3-hydroxymethyl-N-acetylamidine
4-hydroxymethyl-N-acetylamidine
4-hydroxymethylamidine
4-methyl-2-hydroxymethylphenol
30 2-methyl-5-hydroxymethylphenol
4-methyl-3-hydroxymethylphenol
5-methyl-3-hydroxymethylphenol
3-methyl-4-hydroxymethylphenol
2-methyl-4-hydroxymethylphenol
35 3-methyl-5-hydroxymethylphenol

	4-methoxy-3-hydroxymethylphenol
	3-methoxy-4-hydroxymethylphenol
	2-methoxy-4-hydroxymethylphenol
	5-methoxy-3-hydroxymethylphenol
5	3-methoxy-5-hydroxymethylphenol
	2-methoxy-5-hydroxymethylphenol
	2-(1'-hydroxyethyl)phenol
	3-(1'-hydroxyethyl)phenol
	4-(1'-hydroxyethyl)phenol
10	2-(2'-hydroxyethyl)phenol
	3-(2'-hydroxyethyl)phenol
	4-(2'-hydroxyethyl)phenol
	2-(3'-hydroxypropyl)phenol
	3-(3'-hydroxypropyl)phenol
15	4-(3'-hydroxypropyl)phenol
	2-(2'-hydroxypropyl)phenol
	3-(2'-hydroxypropyl)phenol
	4-(2'-hydroxypropyl)phenol
	2-(1'-hydroxypropyl)phenol
20	3-(1'-hydroxypropyl)phenol
	4-(1'-hydroxypropyl)phenol
	3-(4'-hydroxybutyl)phenyl
	4-(4'-hydroxybutyl)phenyl

25 EXAMPLE 38

Following the procedures of Examples 32 to 34, when sodium 4-(2-quinolinylmethyloxy)phenoxide of Example 32, Step C, is replaced by the metal hydroxy, thio or amino salts of the compounds of Table VIII, Example 24, then the corresponding product is prepared. Representative examples of compounds prepared by this invention are shown in Table XIII.

TABLE XIII

35	5-(4-(4-(2-quinolinylmethyloxy)phenoxy)methyl)phenoxy-methyl)tetrazole
	5-(4-(2-(2-quinolinylmethyloxy)phenoxy)methyl)phenoxy-

- methyl) tetrazole
- 5-(3-(2-(2-quinolinylmethyloxy)phenoxy-methyl)phenoxy-methyl) tetrazole
- 5-(2-(4-(2-quinolinylmethyloxy)phenoxy-methyl)phenoxy-methyl) tetrazole
- 5-(2-(3-(2-quinolinylmethyloxy)phenoxy-methyl)phenoxy-methyl) tetrazole
- 5-(2-(2-(2-quinolinylmethyloxy)phenoxy-methyl)phenoxy-methyl) tetrazole
- 10 5-(3-(4-(2-quinolinylmethyloxy)phenoxy-methyl)-2-methoxyphenoxy-methyl) tetrazole
- 5-(3-(4-(2-quinolinylmethyloxy)phenoxy-methyl)-3-methoxyphenoxy-methyl) tetrazole
- 5-(4-(3-(2-quinolinylmethyloxy)phenoxy-methyl)-2-methoxyphenoxy-methyl) tetrazole
- 15 5-(4-(3-(2-quinolinylmethyloxy)phenoxy-methyl)-3-methoxyphenoxy-methyl) tetrazole
- 5-(4-(3-(2-quinolinylmethyloxy)phenoxy-methyl)-3-methylphenoxy-methyl) tetrazole
- 20 5-(4-(4-(2-quinolinylmethyloxy)phenoxy-methyl)-2-methoxyphenoxy-methyl) tetrazole
- 5-(4-(4-(2-quinolinylmethyloxy)phenoxy-methyl)-3-methoxyphenoxy-methyl) tetrazole
- 5-(4-(4-(2-quinolinylmethyloxy)phenoxy-methyl)-3-methylphenoxy-methyl) tetrazole
- 25 5-(4-(4-(2-quinolinylmethyloxy)phenoxy-methyl)-2-methylphenoxy-methyl) tetrazole
- 5-(4-(4-(2-quinolinylmethyloxy)-2-methylphenoxy-methyl)-phenoxy-methyl) tetrazole
- 30 5-(4-(4-(2-quinolinylmethyloxy)-3-methylphenoxy-methyl)-phenoxy-methyl) tetrazole
- 5-(4-(4-(2-quinolinylmethyloxy)-3-methoxyphenoxy-methyl)phenoxy-methyl) tetrazole
- 5-(3-(3-(2-quinolinylmethyloxy)-4-methoxyphenoxy-methyl)phenoxy-methyl) tetrazole
- 35 5-(3-(3-(2-quinolinylmethyloxy)-4-methylphenoxy-methyl)phenoxy-methyl) tetrazole

- 5-(4-(4-(2-quinolinylmethyloxy)-2-methylphenoxy-methyl)-3-methylphenoxy-methyl)tetrazole
- 5-(4-(4-(2-quinolinylmethyloxy)-3-methylphenoxy-methyl)-2-methylphenoxy-methyl)tetrazole
- 5 5-(2-(3-(4-(2-quinolinylmethyloxy)phenoxy-methyl)-phenoxy)ethyl)tetrazole
- 5-(3-(3-(4-(2-quinolinylmethyloxy)phenoxy-methyl)-phenoxy)propyl)tetrazole
- 10 5-(2-(3-(4-(2-quinolinylmethyloxy)phenoxy-methyl)-phenoxy)propyl)tetrazole
- 5-(3-(3-(4-(2-quinolinylmethyloxy)phenoxy-methyl)-phenoxy)butyl)tetrazole
- 5-(4-(4-(2-quinolinylmethyloxy)phenylthiomethyl)-phenoxy-methyl)tetrazole
- 15 5-(4-(4-(2-quinolinylmethyloxy)phenylthiomethyl)-phenylthiomethyl)tetrazole
- 5-(4-(4-(2-quinolinylmethylthio)phenoxy-methyl)-phenoxy-methyl)tetrazole
- 5-(4-(4-(2-quinolinylmethyloxy)phenoxy-methyl)-phenyl-N-acetylaminomethyl)tetrazole
- 20 5-(3-(4-(4-(2-quinolinylmethyloxy)phenoxy-methyl)-phenylthio)butyl)tetrazole
- 5-(3-(3-(4-(2-quinolinylmethyloxy)phenoxy-1'-ethyl)-phenoxy-methyl)tetrazole
- 25 5-(3-(3-(4-(2-quinolinylmethyloxy)phenoxy-2'-propyl)-phenoxy-methyl)tetrazole
- 5-(3-(3-(4-(2-quinolinylmethyloxy)phenoxy-3'-butyl)-phenoxy-methyl)tetrazole

30 EXAMPLE 39

3-(3-(2-QUINOLINYL METHYLOXY) BENZYL OXY) BENZALDEHYDE

When 3-hydroxybenzonitrile in Example 7 is replaced by 3-hydroxybenzaldehyde then the product prepared is 3-[3-(2-quinolinylmethyloxy)benzyloxy]benzaldehyde.

35

EXAMPLE 40

When 3-hydroxybenzaldehyde of Example 39 is replaced by the compounds of Table XIV below, then the corresponding product is obtained.

5

TABLE XIV

2-hydroxybenzaldehyde

3-hydroxybenzaldehyde

4-hydroxybenzaldehyde

2-methyl-3-hydroxybenzaldehyde

10

5-methyl-3-hydroxybenzaldehyde

2-methyl-4-hydroxybenzaldehyde

3-methyl-4-hydroxybenzaldehyde

5-methoxy-3-hydroxybenzaldehyde

4-methoxy-3-hydroxybenzaldehyde

15

2-methoxy-3-hydroxybenzaldehyde

5-carbomethoxy-3-hydroxybenzaldehyde

3-hydroxyphenylacetaldehyde

4-hydroxyphenylacetaldehyde

3-hydroxyphenylpropionaldehyde

20

4-hydroxyphenylpropionaldehyde

3-hydroxyphenylisopropionaldehyde

4-hydroxyphenylisopropionaldehyde

3-hydroxyphenoxycetaldehyde

4-hydroxyphenylthiopropionaldehyde

25

EXAMPLE 41

When 3-(2-quinolinylmethoxy)benzyl chloride of Example 39 is replaced by the compounds prepared by Examples 2-6 and 3-hydroxybenzaldehyde of Example 39 is replaced by the compounds of Table XIV, Example 40, then the corresponding products are obtained.

30

EXAMPLE 423-(3-(2-QUINOLINYLMETHYLOXY) BENZYLOXY) CINNAMYLNITRILE

Sodium hydride (60% oil dispersion, 1.2 g) and diethyl
5 cyanomethylphosphonate (5 ml) are combined and stirred in THF
(50 ml) for 5 minutes. This is then added to a THF solution
of 3-(3-(2-quinolinylmethyloxy)benzyloxy)benzaldehyde (9.59
g). The reaction mixture is stirred for an additional 30
minutes and poured into ice water. The crude product is
10 filtered and chromatographed through a silica gel dry column
using chloroform as the eluant to give 3-(3-(2-quinolinylmethyloxy)benzyloxy)cinnamyl nitrile.

EXAMPLE 43

15 When 3-(3-(2-quinolinylmethyloxy)benzyloxy)benzaldehyde of
Example 42 is replaced by the compounds of Example 41, the
corresponding product is prepared.

When diethylcyanomethylphosphonate in the above Example is
20 replaced by diethylcyanoethylphosphate, diethylcyano-
propylphosphate or diethylcyanoisopropylphosphate then the
corresponding products are obtained.

EXAMPLE 44

25 5-(3-(3-(2-QUINOLINYLMETHYLOXY) BENZYLOXY) STYRYLTETRAZOLE
HYDROCHLORIDE

A mixture of 3-(3-(2-quinolinylmethyloxy)benzyloxy)-
cinnamyl nitrile (0.03 mol), anhydrous aluminum chloride (0.03
mol) and sodium azide (0.09 mol) in THF (30 ml) is stirred
30 and refluxed for 18 hours. Hydrochloric acid (18% HCl 15 ml)
is added and thereafter the reaction mixture is poured into
ice water. The precipitate is collected and then recrystal-
lized from methanol-ethyl acetate to obtain pure 5-(3-(3-(2-
quinolinylmethyloxy)benzyloxy)styryl)tetrazole hydrochloride.

The free base is obtained by treatment of the salt with one equivalent of sodium hydroxide solution followed by removal of sodium chloride and water.

5

EXAMPLE 45

When 3-(3-(2-quinolinylmethyloxy)benzyloxy)cinnamyl nitrile of Example 44 is replaced by the compounds formed in Example 43, then the corresponding product is prepared.

Representative compounds prepared by this invention are described in Table XV.

10

TABLE XV

	5-(4-(3-(2-quinolinylmethyloxy)phenoxy)styryl)tetrazole
15	5-(4-(3-(2-quinolinylmethyloxy)benzyloxy)styryl)- tetrazole
	5-(3-(4-(2-quinolinylmethyloxy)benzyloxy)styryl)- tetrazole
	5-(4-(4-(2-quinolinylmethyloxy)benzyloxy)styryl)- tetrazole
20	5-(4-(3-(2-quinolinylmethyloxy)-4-methylbenzyloxy)- styryl)tetrazole
	5-(4-(3-(2-quinolinylmethyloxy)benzyloxy)3-methyl- styryl)tetrazole
25	5-(3-(3-(2-quinolinylmethylthio)benzyloxy)styryl)- tetrazole
	5-(3-(4-(2-quinolinylmethylthio)phenoxy)styryl)- tetrazole
	5-(3-(4-(2-quinolinylmethyloxy)benzylthio)styryl)- tetrazole
30	5-(3-(4-(3-(2-quinolinylmethyloxy)benzyloxy)phenoxy)- 2-propen-1-yl)tetrazole

EXAMPLE 46

35

3-METHYLCARBOETHOXY-
5-(4-(3-(2-QUINOLINYL METHYLOXY) PHENOXYMETHYL) PHENYL) TETRAZOLE

To a solution of 0.2 g sodium in 30 ml ethanol is first added 1 g of 5-(4-(3-(2-quinolinylmethoxy)phenoxy)methyl)-phenyl)tetrazole and then after 30 minutes 0.6 g of ethylbromoacetate and stirring is continued at 80°C for 16 hours. The solvent is then removed, diluted with water, filtered, washed with ether and dried to give the desired compound, also referred to as ethyl 5-(4-(3-(2-quinolinylmethoxy)phenoxy)methyl)phenyl)tetrazol-3-yl acetate.

When ethylbromoacetate in the above procedure is replaced with N,N-diethyl- α -bromoacetamide, N,N-diethyl-aminoethyl bromide or N-acetylaminoethyl bromide or N-acetyl- α -bromoacetamide, then the corresponding products are obtained.

EXAMPLE 47

5-(4-(3-(2-QUINOLINYL METHYLOXY) PHENOXY METHYL) PHENYL) - TETRAZOL-3-YL) ACETIC ACID

A mixture of 1 g of ethyl [5-(4-(3-(2-quinolinylmethyl-oxy)phenoxy)methyl)phenyl)tetrazol-3-yl]acetate in 5 ml ethanol and 40 ml of 1N NaOH is stirred at 70°C for 4 hours. This is cooled, diluted with water, acidified with acetic acid, filtered, washed with water, and then ethyl acetate to give 5-(4-(3-(2-quinolinylmethoxy)phenoxy)methyl)phenyl)-tetrazol-3-yl acetic acid.

In a similar manner, the substituted tetrazoles of this invention may be prepared.

EXAMPLE 48

4-(4-(2-QUINOLINYL METHYLSULFONYL) PHENOXY METHYL) BENZOIC ACID

A. 4-(4-(2-quinolinylmethylthio)phenoxy)methyl)benzoic acid (4 mmol) in dichloroethene (50 ml) is stirred with m-chloroperbenzoic acid (4 mmol) and solid potassium hydrogen

carbonate (1.0 g). The reaction is assayed by TLC and upon consumption of the starting thio compound, the mixture is filtered, washed with dilute aqueous sodium bisulfite, dried and evaporated to give 4-(4-(2-quinolinylmethylsulfinyl)-
 5 phenoxymethyl)benzoic acid.

B. To 3 mmol of the sulfinyl compound from Step A in acetic acid (40 mmol) is added 30% hydrogen peroxide (2 ml). The mixture is stirred at ambient temperature and assayed by
 10 TLC. Upon disappearance of the sulfinyl starting compound, the reaction mixture is diluted with dichloromethane, washed with dilute aqueous sodium bisulfite and water, dried and evaporated to give 4-(4-(2-quinolinylmethylsulfonyl)-phenoxymethyl)benzoic acid.

15 In a similar manner, the sulfinyl and sulfonyl compounds of this invention may be prepared.

EXAMPLE 49

20 5-(3-METHYL-4-(4-(4-(2-QUINOLINYLMETHYLOXY) BENZYLOXY)-PHENYL) BUTYL) TETRAZOLE

A. 4-benzyloxy- α -methyl-cinnamic acid ethyl ester. To a solution of sodium hydride (60% oil dispersion, 3.1 g) and diethyl 2-phosphonopropionate (15.5 g) in tetrahydrofuran (50
 25 ml) is added dropwise a tetrahydrofuran solution of 4-benzyloxy-benzaldehyde (10.6 g). After stirring at room temperature for 2 hours, the reaction mixture is poured into ice water. The insoluble solid is collected, and used directly in the next step.

30 B. 4-benzyloxy- α -methyl-cinnamic alcohol. Under argon and with stirring, a tetrahydrofuran solution of 4-benzyloxy- α -methyl-cinnamic acid ethyl ester (11.9 g) is added dropwise to a cooled tetrahydrofuran solution of lithium aluminum hydride (2.5 g). The reaction mixture is allowed to stir for
 35 18 hours and afterward, the excess reagent is destroyed in a

conventional manner. The residue which results from the evaporation of the solvent is partitioned in a water/ethyl acetate mixture and from the organic layer, the desired product is obtained. This is used directly in the next step.

5 C. 4-benzyloxy- α -methyl-cinnamyl aldehyde. Manganese dioxide (15 g total) is added portionwise to a dichloromethane solution (100 ml) of 4-benzyloxymethyl-cinnamic alcohol with stirring over a period of one week. After two filtrations, the filtrate is evaporated to yield a
10 gum. Upon treatment with cold hexane, the crude product results which is used directly in the next step.

 D. 5-(p-benzyloxyphenyl)-4-methyl-2,4-pentadienenitrile.
To a solution of sodium hydride (60 % oil dispersion, 1.5 g)
15 and diethyl cyanomethylphosphonate (5.4 g) in tetrahydrofuran (50 ml) is added dropwise a tetrahydrofuran solution of 4-benzyloxy- α -methyl-cinnamyl aldehyde (4.8 g). After stirring at room temperature for 2 hours, the reaction mixture is poured into ice water. The insoluble material is collected
20 and used directly in the next step.

 E. 5-(p-hydroxyphenyl-4-methylvaleronitrile. 5-(p-Benzyloxyphenyl)-4-methyl-2,4-pentadienenitrile (4.3 g) dissolved in ethanol is hydrogenated (0.8 g of 5% palladium
25 over charcoal as catalyst) around 30 psi overnight. After filtering off the catalyst, the solvent is evaporated to give an oil which is used directly in the next step.

 F. 4-methyl-5-(4-(4-(2-quinolinylloxymethyl)benzyloxy)-phenyl)valeronitrile. A reaction mixture of 5-p-
30 hydroxyphenyl-4-methyl-valeronitrile (2.9 g), 4-(2-quinolinylmethoxy)benzyl chloride hydrochloride (6.3 g) and anhydrous potassium carbonate (30 g) in dimethylformamide (60 ml) is stirred and heated (110°C) for 5 hours. Afterward,
35 the solvent is removed under vacuum and the residue is

partitioned in a mixture of chloroform/water. The organic layer is evaporated and the resultant oil is purified on a silica gel dry column (chloroform as eluant) to give product which may be used directly in the next step.

- 5 G. 5-(3-methyl-4-(4-(4-(2-quinolinylmethoxy)-benzyloxy)phenyl)butyl)tetrazole. A mixture of 4-methyl- 5-(4-(4-(2-quinolinylmethoxy)benzyloxy)phenyl)valeronitrile (1.5 g.), sodium azide (3 g), ammonium chloride (1.9 g) in dimethylformamide (20 ml) is stirred and heated at 135°C for 10 18 hours. After cooling, the reaction mixture is poured into ice water and the insoluble material is taken up by chloroform. The residue from the evaporation of chloroform is purified by silica gel dry column (5% methanol in chloroform as eluant) to yield 5-(3-methyl-4-(4-(4-(2-quinolinylmethoxy)benzyloxy)-phenyl)butyl)tetrazole. 15

EXAMPLE 50

- When 2-chloromethylquinoline of Example 49, Part F is replaced by the quinoline compounds of Examples 5 and 6, then 20 the corresponding product is obtained. When the products are treated according to the procedures of Steps F and G, then the corresponding tetrazole products are obtained.

EXAMPLE 51

- 25 When diethyl 2-phosphonopropionate of Example 49, Step A is replaced by the Wittig reagents of Table XVI below then the corresponding products are obtained.

TABLE XVI

- 30 diethyl 2-phosphonoacetate
diethyl 2-phosphonopropionate
diethyl 3-phosphonopropionate
diethyl 4-phosphonobutyrate
diethyl 3-phosphonobutyrate
35 diethyl 2-phosphonobutyrate
diethyl 5-phosphonopentanoate

diethyl 4-phosphonopentanoate
 diethyl 3-phosphonopentanoate
 diethyl 4-phosphono-3-methylbutyrate
 diethyl 4-phosphono-2,3-dimethylbutyrate
 5 diethyl 5-phosphono-4-methylpentanoate
 diethyl 5-phosphono-3,4-dimethylpentanoate
 diethyl 4-phosphono-3,3-dimethylbutyrate
 diethyl 4-phosphono-3-phenylbutyrate
 diethyl 4-phosphono-3-benzylbutyrate
 10 diethyl 3-phosphono-2,2-dimethylpropionate
 diethyl 4-phosphono-2-propylbutyrate
 diethyl 4-phosphono-3-propylbutyrate
 diethyl 3-phosphonomethylhexanoate
 diethyl 4-phosphonoheptanoate

15 EXAMPLE 52

When diethylcyanomethylphosphonate of Example 49, Step D is replaced by the Wittig reagents of Table XVII below then the corresponding products are obtained.

20 TABLE XVII

diethyl 2-phosphonoacetonitrile
 diethyl 3-phosphonopropionitrile
 diethyl 2-phosphonopropionitrile
 diethyl 4-phosphonobutyronitrile
 25 diethyl 3-phosphonobutyronitrile
 diethyl 2-phosphonobutyronitrile
 diethyl 5-phosphonopentanitrile
 diethyl 4-phosphonopentanitrile
 diethyl 3-phosphonopentanitrile
 30 diethyl 2-phosphonopentanitrile
 diethyl 4-phosphono-5-phenylpentanitrile
 diethyl 4-phosphono-3-phenylbutyronitrile
 diethyl 4-phosphono-5-cyclopropylpentanitrile
 diethyl 4-phosphonoheptanitrile
 35 diethyl 4-phosphonoheptanitrile
 diethyl 4-phosphono-5-carbethoxypentanitrile

diethyl 4-phosphono-3-methylenebutynitrile
diethyl 4-phosphono-3-ethylidenebutynitrile
diethyl 1-phosphonomethyl-1-cyanoethylcyclopropane
diethyl 1-phosphonomethyl-1-cyanomethylcyclobutane
5 diethyl 1-phosphonomethyl-2-cyanomethylcyclobutane
diethyl 1-phosphonomethyl-2-cyanomethylcyclopentane

EXAMPLE 53

When diethyl 2-phosphonopropionate of Example 49, Step A is
10 replaced by the Wittig reagents of Table XVII, Example 52,
then the corresponding products are obtained. When these
products are treated according to the procedure of Example
50, then the corresponding product is obtained.

15 EXAMPLE 54

When 4-hydroxy-3-methoxybenzoate of Example 14 is replaced
with 3-hydroxymethylphenol, then the product prepared is 3-
(3-(2-quinolinylmethyloxy)benzyloxy)benzyl alcohol.

20 EXAMPLE 55

When 4-hydroxy-3-methoxybenzoate of Example 14 is replaced
with the compounds of Table XVIII below and 3-(2-quinolinyl-
methyloxy)benzyl chloride is replaced by the compounds of
Example 6, then the corresponding products are prepared.

25 TABLE XVIII

1,2-dihydroxybenzene
1,3-dihydroxybenzene
1,4-dihydroxybenzene
2-mercaptophenol
30 3-mercaptophenol
4-mercaptophenol
1,3-dimercaptobenzene
3-hydroxymethylphenol
3-hydroxyethylphenol
35 3-mercaptomethylphenol
4-hydroxymethylphenol

4-hydroxyethylphenol
 2-methylresorsinol
 5-methylresorsinol
 5-methyl-1,4-dihydroxybenzene

5

EXAMPLE 565-(3-CHLOROPROPYL)TETRAZOLE

A mixture of 3.5 g of 4-chlorobutyronitrile, 2.3 g of sodium azide and 1.9 g of ammonium chloride in 50 ml of dimethyl-formamide is stirred at 140°C for 20 hours. The reaction mixture is poured onto ice, basified with 1N sodium hydroxide and extracted twice with ethyl acetate. The aqueous fraction is acidified with acetic acid and extracted with ethylacetate. Evaporation of the ethyl acetate gives 5-(3-chloropropyl)-tetrazole which is used directly in the next step.

EXAMPLE 57

When 4-chlorobutyronitrile of Example 56 above is replaced by the nitriles of Table XIX below then the corresponding tetrazole product is obtained.

TABLE XIX

	chloroacetonitrile
25	bromoacetonitrile
	3-chloropropionitrile
	4-chlorobutyronitrile
	5-chloropentanitrile
	6-chlorohexanonitrile
30	2-chloropropionitrile
	2-methyl-3-chloropropionitrile
	2-chlorobutyronitrile
	3-chlorobutyronitrile
	4-methyl-5-chloropentanitrile
35	2-methyl-3-chloropropionitrile
	3-benzyl-4-chlorobutyronitrile

- 3-carbethoxymethyl-4-chlorobutyronitrile
3-methoxymethyl-4-chlorobutyronitrile
2,3-dimethyl-4-chloropentanitrile
3,3-dimethyl-4-chloropentanitrile
5 spiro-(3,3-cyclopropane)-4-chlorobutyronitrile
1-chloromethyl-2-cyanomethylcyclobutane
1-chloromethyl-2-cyanomethylcyclohexane
3-cyclopropylmethyl-4-chlorobutyronitrile
3-dimethylaminomethyl-4-chlorobutyronitrile
10 3-methylene-4-chlorobutyronitrile
3-propylidene-4-chlorobutyronitrile

EXAMPLE 58

- 15 5-(4-(3-(3-(2-QUINOLINYLMETHYLOXY) BENZYLOXY) PHENYL) BUTYL) -
TETRAZOLE

- A mixture of (0.014 mol) 3-(3-(2-quinolinylmethyloxy)-benzyloxy)benzyl alcohol (0.14 mol) 5-(3-chloropropyl)-
20 tetrazole and 2 g (0.036 mol) KOH in 5 ml water and 50 ml
ethanol is heated over a steam bath for a period of 3 hours.
Reaction mixture is concentrated to dryness and slurried into
water and extracted with methylene chloride. The methylene
chloride extract is washed with water, dried over MgSO_4 and
concentrated under reduced pressure to obtain solid which is
25 passed through a silica gel column using hexane/ethyl acetate
as eluent. Evaporation of eluent gives 5-(4-(3-(3-(2-
quinolinylmethyloxy)benzyloxy)phenyl)butyl)tetrazole.

EXAMPLE 59

- 30 When 3-(3-(2-quinolinylmethyloxy)benzyloxy)benzyl alcohol
of Example 58 is replaced by the compounds prepared by
Examples 54 and 55 and 5-(3-chloropropyl)tetrazole is
replaced by the compounds prepared by Example 57, then the
corresponding product is obtained.

TABLE XX

	5-(4-(4-(3-(2-quinolinylmethyloxy)benzyloxy)phenyl)-butyl)tetrazole
5	5-(3-(4-(3-(2-quinolinylmethyloxy)benzyloxy)phenyl)-butyl)tetrazole
	5-(3-(4-(4-(2-quinolinylmethyloxy)benzyloxy)phenyl)-butyl)tetrazole
10	5-(2-(3-(3-(2-quinolinylmethyloxy)benzyloxy)phenyl)-propyl)tetrazole
	5-(3-(3-(3-(2-quinolinylmethylthio)benzyloxy)phenyl)-butyl)tetrazole
	5-(3-(3-(3-(2-quinolinylmethyloxy)benzyloxy)phenyl)-butyl)tetrazole
15	5-(3-(3-(3-(2-quinolinylmethyloxy)benzylthio)phenyl)-butyl)tetrazole
	5-(4-(3-(3-(2-quinolinylmethyloxy)benzyloxy)phenyl)-butyl)tetrazole
20	5-(3-(3-(3-(2-quinolinylmethyloxy)phenoxy)phenyl)-butyl)tetrazole

EXAMPLE 60

When 3-hydroxybenzonitrile in Example 7 is replaced by 3-hydroxybenzaldehyde then the product prepared is 3-(2-quinolinylmethyloxy)benzaldehyde.

EXAMPLE 61

When 3-hydroxybenzaldehyde in Example 60 is replaced by the compounds of Table XIV, Example 40 and 3-(2-quinolinylmethyloxy)benzyl chloride is replaced by the chlorides prepared in Examples 5 and 6, then the corresponding product is prepared.

EXAMPLE 62

35 5-(4-(3-(2-QUINOLINYL METHYLOXY) BENZOYLMETHYL) PHENYL) TETRAZOLE

A. 2-(3-(2-quinolinylmethyloxy)phenyl)-1,3-dithiane. A
1M solution of 3-(2-quinolinylmethyloxy)benzaldehyde (0.01

mol) in chloroform is combined with an equimolar amount of 1,3 propane-dithiol at -20°C . Dry HCl gas is slowly passed through the solution for 5-10 minutes. The reaction mixture is then allowed to come to room temperature. After 3 hours, the reaction mixture is worked up by successively washing with water, 10% aqueous KOH and water and drying over K_2CO_3 . Evaporation of the solvent furnishes the desired product which is purified by column chromatography to give product which is used directly in the next step.

10 B. 2-(3-(2-quinolinylmethyloxy)phenyl)-2-(p-cyanobenzyl)-1,3-dithiane. To a 0.2M THF solution of the 2-(3-(2-quinolinyl-methyloxy)phenyl)-1,3-dithiane (0.01 mol) under N_2 is added a 5% excess of N-butyl lithium in N-hexane (2.5M) at a rate of 3-5 ml/min at -78°C . After 3 hours, 4-cyanobenzyl-chloride (0.01 mol in 20 ml of THF) is added dropwise over a period of 10 minutes. Let stir 3 hours at -78°C and then allow the reaction mixture to come to 0°C slowly. The mixture is poured into 3 volumes of water, extracted with chloroform furnishing an organic solution which is washed twice with water, 7% aqueous KOH and again with water. The organic layer is dried over K_2CO_3 and is concentrated. The crude product is purified by column chromatography to give the desired product which is used directly in the next step.

25 C. 4-(3-(2-quinolinylmethyloxy)benzoylmethyl)benzonitrile. To a solution of 2-(3-(2-quinolinylmethyloxy)-1,3-dithiane (1.0 mmol) in 80% aqueous acetonitrile (10 ml) is added mercuric chloride (2.2 mmol) as a solution in the same solvent mixture. Mercuric oxide (1.1 mmol) is then added to buffer the reaction mixture near $\text{pH}=7$. The dithiane - mercuric chloride complex separates as a white precipitate. The reaction mixture is refluxed under nitrogen for 5 hours, then cooled and filtered through Super Gel. The filter cake is washed thoroughly with 1:1 hexane-dichloromethane. The organic phase is washed with 5 M aqueous ammonium acetate,

water and brine. The organic phase is then dried with MgSO_4 , and is concentrated to give the crude product which is purified by column chromatography to give 4-(3-(2-quinolinylmethoxy)benzoylmethyl)benzonitrile.

5 D. 5-(4-(3-(2-quinolinylmethoxy)benzoylmethyl)-phenyl)tetrazole. A heterogenous mixture of 4-(3-(2-quinolinylmethoxy)benzoylmethyl)benzonitrile (1.35 mmol). NaN_3 (6.77 mmol), pyridinium hydrochloride (6.77 mmol) in DMF (3 ml) is heated at 100°C for 3 hours under nitrogen. The
 10 reaction mixture is poured into water and the product is collected on a filter. Recrystallization from EtOAc - DMF gives 5-(4-(3-(2-quinolinylmethoxy)benzoylmethyl)phenyl)-tetrazole.

15 EXAMPLE 63

When 3-(2-quinolinylmethoxy)benzaldehyde in Example 62, Step A is replaced by the aldehydes of Example 61, and 4-cyanobenzyl chloride of Example 62, Step B is replaced by the compounds of Table X, Example 29 or Table VII, Example 23,
 20 then the corresponding products are obtained. Representative compounds prepared by this invention are shown in Table XXI.

TABLE XXI

25 5-(4-(4-(2-quinolinylmethoxy)benzoylmethyl)phenyl)tetrazole
 5-(4-(3-(2-quinolinylmethoxy)benzoylmethyl)benzyl)tetrazole
 5-(3-(4-(3-(2-quinolinylmethoxy)benzoylmethyl)phenyl)-propyl)tetrazole
 5-(3-(3-(2-quinolinylmethylthio)benzoylmethyl)phenyl)-
 30 tetrazole
 5-(4-(3-(2-quinolinylmethoxy)benzoylethyl)benzyl)tetrazole

EXAMPLE 645-(3-(3-(2-QUINOLINYLMETHYLOXY)BENZOYLAMINO)PHENYL)TETRAZOLE

A. 3-(2-quinolinylmethyloxy)benzoic acid. A mixture of
5 28.16 g (0.132 mol) of 2-quinolinylmethyl chloride HCl, 18 g
(0.132 mol) of 3-hydroxybenzoic acid and 39.6 g of potassium
carbonate in 110 ml of DMF is heated at 70°C overnight. The
reaction mixture is poured into water, and the precipitated
product is collected, filtered and dried to give 3-(2-
10 quinolinylmethyloxy)benzoic acid.

B. 3-(2-quinolinylmethyloxy)benzoic acid chloride. A
mixture of 15.6 g (0.1 mol) of 3-(2-quinolinylmethyloxy)-
benzoic acid and 11.9 g (0.1 mol) of thionyl chloride is
15 refluxed for 4 hours. The reaction mixture is then
evaporated to dryness at room temperature and used directly
in the next step.

C. 3-(3-(2-quinolinylmethyloxy)benzoylamino)benzonitrile.
20 A solution of 3-aminobenzonitrile (10 mmol) in 50 ml of
chloroform and triethylamine (11 mmol) is added to a solution
of 10 mmol of 3-(2-quinolinylmethyloxy)benzoic acid chloride
in 20 ml of chloroform over a period of 10 minutes. The
reaction is stirred at room temperature for 2 hours and is
25 poured into water and then extracted into chloroform. The
organic solution is dried and evaporated to give 3-(3-(2-
quinolinylmethyloxy)benzoylamino)-benzonitrile.

D. 5-(3-(3-(2-quinolinylmethyloxy)benzoylamino)phenyl)-
30 tetrazole. A mixture of 10 mmol of 3-(3-(2-quinolinylmethyloxy)benzoylamino)benzonitrile, 50 mmol of sodium azide, and
50 mmol of pyridine HCl in 30 ml of DMF is heated at 100°C
for 2 days. The reaction mixture is poured into water, and
the product is collected on a filter. Recrystallization from
35 ethyl acetate and DMF gives 5-(3-(3-(2-quinolinylmethyloxy)-
benzoylamino)phenyl)tetrazole.

In a similar manner, the compounds of this invention

$$\begin{array}{c} \text{O} \quad \text{R}_1 \\ | \quad | \\ \text{---C---N---} \end{array}$$
 where B is

may be made.

5

EXAMPLE 65

5-(3-(3-(2-QUINOLINYLMETHYLOXY)-
ANILINOCARBONYL) PHENYL) TETRAZOLE

When the procedure of Example 64 is followed and 3-(2-
 10 quinolinylmethoxy)aniline is used in place of 3-amino-
 benzonitrile and 3-cyanobenzoic acid is used in place of 3-
 (2-quinolinylmethoxy) benzoic acid, then the product
 prepared is 5-(3-(3-(2-quinolinylmethoxy)anilinocarbonyl)-
 phenyl)tetrazole.

15 In a similar manner, the compounds of this invention

$$\begin{array}{c} \text{R}_1 \quad \text{O} \\ | \quad | \\ \text{---N---C---} \end{array}$$
 where B is

may be made.

20 The methods described above are used to prepare the
 following compounds of this invention.

5-[2-(4-(2-Quinolinylmethoxy)phenoxy)methyl]benzyl]tetrazole
 (M.P. 108-111°C)

CALC: C, 59.87; H, 5.96; N, 13.96

25 FOUND: C, 59.67, 60.01; H, 5.62, 5.63; N, 13.73, 13.77

5-[4-Methoxy-3-(3-(2-quinolinylmethoxy)phenoxy)methyl)-
 phenyl]tetrazole (M.P. 184-87°C)

CALC: C, 67.63; H, 4.88; N, 15.78

30 FOUND: C, 67.18; H, 5.13; N, 15.40

5-[3-(4-(2-quinolinylmethoxy)phenoxy)methyl]phenyl]tetrazole
 (M.P. 176-177°C)

CALC: C, 69.63; H, 4.75; N, 16.92

35 FOUND: C, 69.58, 69.64; H, 5.00, 4.98; N, 16.66, 16.63

- 5-[3-Methoxy-4-(4-(2-quinolinylmethyloxy)benzyloxy)phenyl]tetrazole (M.P. 195-97°C)
CALC: C, 67.63; H, 4.88; N, 15.77
FOUND: C, 67.27; H, 4.89; N, 15.41
- 5 5-[4-(3-(2-quinolinylmethyloxy)phenoxy-methyl)-3-methoxyphenyl]-tetrazole (M.P. 189-91°C)
CALC: C, 66.95; H, 4.95; N, 15.61
FOUND: C, 66.48; H, 5.14; N, 14.93
- 10 5-[3-(4-(2-quinolinylmethyloxy)phenoxy-methyl)benzyl]tetrazole (M.P. 139-44°C)
CALC: C, 70.53; H, 5.03; N, 16.45
FOUND: C, 70.33, 70.54; H, 5.25, 5.36; N, 16.38, 16.41
- 15 5-[4-(4-(2-quinolinylmethyloxy)phenoxy-methyl)benzyl]tetrazole (M.P. 167-71°C)
CALC: C, 67.33; H, 5.31; N, 15.70
FOUND: C, 67.54, 67.67; H, 5.33, 5.33; N, 15.48, 15.52
- 20 5-[4-Methoxy-3-(4-(2-quinolinylmethyloxy)phenylmethyloxy)-phenyl]tetrazole (M.P. 210-13°C)
CALC: C, 68.33; H, 4.82; N, 4.90
FOUND: C, 68.32; H, 4.90; N, 14.79
- 25 4-[3-(2-Quinolinylmethyloxy)phenoxy-methyl]phenoxyacetic acid (M.P. 164 (dec))
CALC: C, 69.27; H, 5.35; N, 3.23
FOUND: C, 69.53, 69.65; H, 5.11, 5.05; N, 3.21, 3.12
- 30 5-[2-(4-(2-Quinolinylmethyloxy)phenoxy-methyl)phenoxy-methyl]tetrazole (M.P. 183-85°C)
CALC: C, 65.63; H, 5.08; N, 15.31
FOUND: C, 65.77, 65.52; H, 4.99, 5.03; N, 14.92, 15.03

- 4-[4-(2-Quinolinylmethyloxy)phenoxyethyl]phenoxyacetic acid
(176°C (dec))
CALC: C, 71.50; H, 5.16; N, 3.34
FOUND: C, 71.10, 71.17; H, 5.27, 5.33; N, 3.37, 3.34
- 5 4-[3-(2-Quinolinylmethyloxy)phenoxyethyl]phenylacetic acid
(M.P. 158-60°C)
CALC: C, 75.17; H, 5.30; N, 3.51
FOUND: C, 74.89; H, 5.36; N, 3.37
- 10 2-[3-(3-(2-Quinolinylmethyloxy)phenoxyethyl)phenoxy]-
pentanoic acid (M.P. 133-35°C)
CALC: C, 73.51; H, 5.95; N, 3.06
FOUND: C, 73.35, 73.60; H, 5.95, 5.98; N, 3.08, 3.05
- 15 2-[3-(2-Quinolinylmethyloxy)phenoxyethyl]phenoxyacetic acid
(M.P. 169-172°C)
CALC: C, 72.28; H, 5.10; N, 3.37
FOUND: C, 69.34, 69.69; H, 5.10, 5.13; N, 3.00, 3.08
CALC: C, 69.27; H, 5.35; N, 3.23 (as Hydrate)
- 20 2-[4-(2-Quinolinylmethyloxy)phenoxyethyl]cinnamic acid
(M.P. 175-178°C)
CALC: C, 75.90; H, 5.14; N, 3.40
FOUND: C, 73.92; H, 5.20; N, 3.01
CALC: C, 74.27; H, 5.27; N, 3.33 (as Hydrate)
- 25 6-Acetyl-2-propyl-3-[3-(2-quinolinylmethyloxy)-
benzyloxy]phenoxyacetic acid (M.P. 153-58°C)
CALC: C, 72.13; H, 5.85; N, 2.90
FOUND: C, 71.68, 72.08; H, 5.88, 5.83; N, 2.65, 2.70
- 30 2-[2-(4-(7-Chloroquinolin-2-ylmethyloxy)-
phenoxyethyl)phenoxy]propionic acid (M.P. 169-173°C)
CALC: C, 67.32; H, 4.78; N, 3.02; Cl, 7.64
FOUND: C, 65.18; H, 4.90; N, 2.84; Cl, 8.33
CALC: C, 65.41; H, 4.96; N, 2.93; Cl, 7.42 (as HYDRATE)

- 2-[4-(2-Quinolinylmethyloxy)phenoxyethyl]phenylacetic acid
(M.P. 181-83°C)
CALC: C, 75.17; H, 5.30; N, 3.51
FOUND: C, 75.12, 74.96; H, 5.50, 5.49; N, 3.16, 3.16
- 5 3-[3-(2-Quinolinylmethyloxy)phenoxyethyl]phenoxyacetic acid
(M.P. 146-51°C)
CALC: C, 72.28; H, 5.10; N, 3.37
FOUND: C, 71.82, 71.80; H, 5.24, 5.23; N, 2.98, 3.00
CALC: C, 71.50; H, 5.16; N, 3.34 (as HYDRATE)
- 10 2-[4-(2-Quinolinylmethyloxy)phenoxyethyl]phenoxyacetic acid
(M.P. 153-57°C)
CALC: C, 72.28; H, 5.10; N, 3.37
FOUND: C, 72.30, 71.72; H, 5.39, 5.30; N, 2.94, 2.89
- 15 5-[2-(4-(7-Chloroquinolin-2-ylmethyloxy)-
phenoxyethyl)benzyl]tetrazole (M.P. 159-63°C)
CALC: C, 65.57; H, 4.40; N, 15.29
FOUND: C, 64.16; H, 4.72; N, 14.98
CALC: C, 64.30; H, 4.53; N, 14.99 (as HYDRATE)
- 20 2-Carbomethoxy-5-[3-(2-quinolinylmethyloxy)-
phenoxyethyl]phenoxyacetic acid (M.P. 187-89°C)
CALC: C, 68.49; H, 4.90; N, 2.95
FOUND: C, 66.71; H, 4.96; N, 2.70
CALC: C, 66.59; H, 5.07; N, 2.87 (as HYDRATE)
- 25 2-[3-(2-Quinolinylmethyloxy)phenoxyethyl]-6-
methylphenoxyacetic acid (M.P. 149-53°C)
CALC: C, 72.71; H, 5.40; N, 3.26
FOUND: C, 71.23; H, 5.46; N, 3.08
CALC: C, 71.22; H, 5.51; N, 3.19 (as HYDRATE)

2-[3-(3-(2-Quinolinylmethyloxy)phenoxy-methyl)phenoxy]glutaric acid (M.P. 129-30°C)

CALC: C, 69.00; H, 5.17; N, 2.87

FOUND: C, 58.19; H, 4.93; N, 2.23

5 CALC: C, 58.23; H, 5.17; N, 2.43 (as HYDRATE)

2-[3-(2-Quinolinylmethyloxy)phoxymethyl]benzylmalonic acid (M.P. 164-65°C)

CALC: C, 70.89; H, 4.08; N, 3.06

10 FOUND: C, 70.51, 70.61; H, 5.03, 5.24; N, 3.03, 2.90

2-[2-(3-(Quinolinylmethyloxy)phoxymethyl)phenoxy]pentanoic acid (M.P. 118-20°C)

CALC: C, 73.51; H, 5.95; N, 3.06

15 FOUND: C, 73.26; H, 6.07; N, 2.79

2-[4-(2-Quinolinylmethyloxy)phoxymethyl]-6-methylphenoxy acetic acid (M.P. 151-53°C)

CALC: C, 72.71; H, 5.40; N, 3.26

20 FOUND: C, 71.41; H, 5.58; N, 3.03

CALC: C, 71.22; H, 5.51; N, 3.19 (as HYDRATE)

2-[2-(4-(2-Quinolinylmethyloxy)phenoxy-methyl)phenoxy]pentanoic acid (M.P. 85-92°C)

25 CALC: C, 73.51; H, 5.95; N, 3.06

FOUND: C, 71.73, 71.79; H, 5.96, 5.91; N, 3.06, 2.83

CALC: C, 72.09; H, 6.05; N, 3.00 (as HYDRATE)

30 2-Carbomethoxy-5-[4-(2-quinolinylmethyloxy)-phoxymethyl]phenoxyacetic acid (M.P. 149-51°C)

CALC: C, 68.49; H, 4.90; N, 2.95

FOUND: C, 68.00, 68.08; H, 4.98, 5.04; N, 2.90, 2.90

2-[2-(4-(2-Quinolinylmethyloxy)phenoxy-methyl)phenoxy]propionic acid (M.P. 161-64°C)

CALC: C, 72.71; H, 5.40; N, 3.26

FOUND: C, 70.96, 71.10; H, 5.51, 5.58; N, 3.08, 3.10

5 CALC: C, 71.22; H, 5.52; N, 3.19 (as HYDRATE)

2-[2-(3-(2-Quinolinylmethyloxy)phenoxy-methyl)phenoxy]glutaric acid (M.P. 83°C dec)

CALC: C, 68.98; H, 5.17; N, 2.87

10 FOUND: C, 64.10, 63.75; H, 4.89, 4.92; N, 2.64, 2.69

CALC: C, 63.74; H, 5.63; N, 2.65 (as HYDRATE)

2-(3-[2-Quinolinylmethyloxy]benzyloxy)phenoxyacetic acid (M.P. 153-55°C)

15 CALC: C, 72.28; H, 5.10; N, 3.37

FOUND: C, 71.75; H, 5.14; N, 3.38

CALC: C, 71.50; H, 5.16; N, 3.34 (as HYDRATE)

20 2-(2-[4-(2-Quinolinylmethyloxy)phenoxy-methyl]-4-chlorophenoxy)propionic acid (M.P. 196-99°C)

CALC: C, 67.32; H, 4.78; N, 3.02

FOUND: C, 67.40, 67.43; H, 4.89, 4.94; N, 3.01, 3.13

25 2-(2-[3-(2-Quinolinylmethyloxy)phenoxy-methyl]-4-chlorophenoxy)propionic acid (M.P. 169-71°C)

CALC: C, 67.32; H, 4.78; N, 3.02

FOUND: C, 65.47; H, 5.31; N, 2.78

CALC: C, 65.41; H, 4.96; N, 2.93 (as HYDRATE)

30 2-(2-[3-(2-Quinolinylmethyloxy)phenoxy-methyl]-4-chlorophenoxy)pentanoic acid (M.P. 144-45°C)

CALC: C, 68.36; H, 5.33; N, 2.85

FOUND: C, 67.74, 67.86; H, 5.39, 5.47; N, 2.91, 2.84

CALC: C, 67.74; H, 5.38; N, 2.82 (as HYDRATE)

2-(2-[4-(2-Quinolinylmethyloxy)phenoxy-methyl]-4-chlorophenoxy)pentanoic acid (M.P. 155-56°C)

CALC: C, 68.36; H, 5.33; N, 2.85

FOUND: C, 65.96; H, 5.59; N, 2.66

5 CALC: C, 65.95; H, 5.53; N, 2.75 (as HYDRATE)

2-(2-[4-(2-Quinolinylmethyloxy)phenoxy-methyl]-4-chlorophenoxy)pentanoic acid (M.P. 155-56°C)

CALC: C, 68.36; H, 5.33; N, 2.85

10 FOUND: C, 66.15; H, 5.58; N, 2.68

CALC: C, 65.95; H, 5.53; N, 2.75 (as HYDRATE)

2-(2-[4-(2-Quinolinylmethyloxy)phenoxy-methyl]-6-chlorophenoxy)pentanoic acid (M.P. 161-62°C)

15 CALC: C, 68.36; H, 5.33; N, 2.85

FOUND: C, 68.15; H, 5.36; N, 2.72

2-(2-[3-(2-Quinolinylmethyloxy)phenoxy-methyl]-6-chlorophenoxy)pentanoic acid (M.P. 169-70°C)

20 CALC: C, 68.36; H, 5.33; N, 2.85

FOUND: C, 68.10; H, 5.39; N, 2.72

2-(2-[3-(2-Quinolinylmethyloxy)phenoxy-methyl]-6-chlorophenoxy)-4-methylpentanoic acid (M.P. 164-66°C)

25 CALC: C, 68.84; H, 5.58; N, 2.77

FOUND: C, 68.84; H, 5.70; N, 2.69

2-(2-[4-(2-Quinolinylmethyloxy)phenoxy-methyl]-6-chlorophenoxy)-4-methylpentanoic acid (M.P. 167-69°C)

30 CALC: C, 68.84; H, 5.58; N, 2.77

FOUND: C, 68.78; H, 5.67; N, 2.68

5-[3-(3-(2-quinolinylmethyloxy)benzyloxy)-4-methoxy-phenyl]tetrazole (M.P. 204-07°C)

35 CALC: C, 67.63; H, 4.88; N, 15.78

FOUND: C, 67.11; H, 5.15; N, 15.86

N-[3-Methoxy-4-(3-(2-quinolinylmethyloxy)benzyloxy)-benzoyl]benzene sulphonamide hydrochloride (M.P. dec.88)

CALC: C, 62.99; H, 4.60; N, 4.74

FOUND: C, 63.88; H, 5.13; N, 4.80

5 5-Carboxy-2-(3-(2-quinolinylmethyloxy)phenoxy)methyl)phenoxy acetic acid (M.P. 226-28°C)

CALC: C, 61.90; H, 5.18; N, 2.77

FOUND: C, 61.62; H, 5.11; N, 2.67

10 5-[3-Methoxy-4-(3-(2-quinolinylmethyloxy)-benzyloxy)phenyl]tetrazole (M.P. 204-05°C)

CALC: C, 67.67; H, 5.14; N, 15.87

FOUND: C, 67.63; H, 4.88; N, 15.78

15 5-(4-(3-(2-Quinolinylmethyloxy)benzyloxy)phenyl)tetrazole (M.P. 233-36°C)

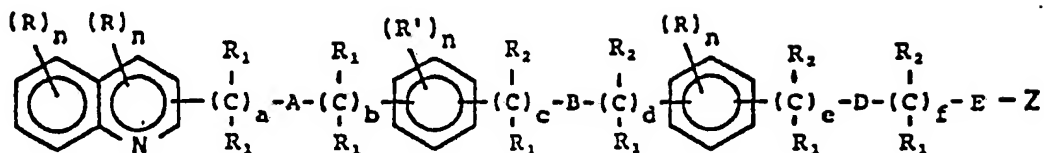
CALC: C, 69.58; H, 4.73; N, 16.91

FOUND: C, 69.59; H, 4.89; N, 16.91

20 Using a combination of the above Examples, various compounds may be made within the scope of this invention.

WE CLAIM:

1. A compound of the formula



5 where:

A is O or S;

B is O, S, SO, SO₂ NR₁, $\text{-}\overset{\text{O}}{\parallel}\text{C-}$, $\text{-}\overset{\text{R}_1}{\text{N}}\text{-}$, $\text{-}\overset{\text{O}}{\parallel}\text{C-}$ or $\text{-}\overset{\text{O}}{\parallel}\text{C-}\overset{\text{R}_1}{\text{N-}}$;10 D is O, S, NR, $\text{-}\overset{\text{R}_1}{\text{C}}=\overset{\text{R}_1}{\text{C-}}$ or a chemical bond;E is a chemical bond or $\text{-}\overset{\text{R}_1}{\text{C}}=\overset{\text{R}_1}{\text{C-}}$;

a is 0-2;

b is 0-1;

15 c is 0-4;

d is 0-5;

e is 0-4;

f is 0-5;

n is 0-2;

20 R is independently hydrogen, alkyl, hydroxy, alkoxy, carboxy, carbalkoxy, halo, nitro, haloalkyl, cyano or acyl;

R' is independently hydrogen, alkyl, hydroxy, alkoxy, halo or haloalkyl;

25 R₁ is independently hydrogen, alkyl or aralkyl;R₂ is $\text{-(CH}_2\text{)}_x\text{-X}$, where x is 0-3;

X is hydrogen, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, mono- and di-alkylamino, aralkylamino, acylamino, carbamyl, carboxy, carbalkoxy, tetrazolyl, or acylsulfonamido;

30 vicinal R₂ groups together may be $\text{(CH}_2\text{)}_y\text{-}$ where y is

1-4, thus forming a 3-6 membered ring;

geminal R₁ and R₂ groups may together form a spiro

substituent, $-(CH_2)_z-$, where z is 2 to 5;

geminal R_1 or R_1 and R_2 groups may together form an alkylidenyl substituent, $=CHR_1$;

5

Z is $-COOR_1$, CN , $-\overset{O}{\parallel}CNHSO_2R_3$, $-\overset{O}{\parallel}CN(R_1)_2$, $-OR_1$, tetrazolyl or substituted tetrazolyl where the substituent may be alkyl, carboxyalkyl or carbalkoxyalkyl; and

R_3 is hydrogen, alkyl, haloalkyl, phenyl or benzyl;

10

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 where:

A is O or S ;

B is O or S ;

15

n is 0-1;

$a + b$ is 1;

$c + d$ is 1-2;

$e + f$ is 0-5;

R and R' are hydrogen, alkyl or alkoxy;

20

R_1 is hydrogen or alkyl;

R_2 is $-(CH_2)_x-X$ where x is 0-3 and X is hydrogen or alkyl; and

Z is $-COOR_1$, $-CN$, $-\overset{O}{\parallel}CNHSO_2R_3$, $-\overset{O}{\parallel}CN(R_1)_2$ or tetrazolyl.

25

3. A compound according to claim 2 where:

A and B are O ;

n is 0;

$c + d$ is 1; and

30

Z is $-COOR_1$, $-CN$ or tetrazolyl.

4. A compound according to claim 3 where:

a is 1; b is 0; c is 1; and d is 0.

35

5. A compound according to claim 4 where:

D is O ; and E is a chemical bond.

6. A compound according to claim 4 where:
D is S; and E is a chemical bond.
7. A compound according to claim 4 where:
5 e + f is 0; D is a chemical bond; and
E is a chemical bond.
8. A compound according to claim 4 where:
e + f is 1-5; D is a chemical bond; and
10 E is a chemical bond.
9. A compound according to claim 4 where:
D is O; and
15 E is $\begin{array}{c} R_1 \\ | \\ -C \end{array} = \begin{array}{c} R_1 \\ | \\ C- \end{array}$.
10. A compound according to claim 4 where:
D is a chemical bond or $\begin{array}{c} R_1 \\ | \\ -C \end{array} = \begin{array}{c} R_1 \\ | \\ C- \end{array}$; and
20 E is $\begin{array}{c} R_1 \\ | \\ -C \end{array} = \begin{array}{c} R_1 \\ | \\ C- \end{array}$.
11. A compound according to claim 3 where:
a is 1; b is 0; c is 0; and d is 1.
- 25 12. A compound according to claim 2 where:
is 1; b is 0; c is 0; and d is 2.
13. A compound according to claim 11 where:
D is O; and E is a chemical bond.
- 30 14. A compound according to claim 11 where:
c + f is 0; D is a chemical bond; and E is a chemical bond.
15. A compound according to claim 13 where e + f is 1-5.

16. A compound according to claim 7 which is
5-(3-(3-(2-quinolinylmethyloxy)benzyloxy)phenyl)tetrazole or
a pharmaceutically acceptable salt thereof.
- 5 17. A compound according to claim 7 which is
5-[4-(3-(2-quinolinylmethyloxy)phenoxyethyl)phenyl]tetrazole
or a pharmaceutically acceptable salt thereof.
- 10 18. A compound according to claim 7 which is
5-[3-methoxy-4-(3-(2-quinolinylmethyloxy)benzyloxy)-
phenyl]tetrazole or a pharmaceutically acceptable salt
thereof.
- 15 19. A compound according to claim 7 which is
5-[4-methoxy-3-(3-(2-quinolinylmethyloxy)benzyloxy)-
phenyl]tetrazole or a pharmaceutically acceptable salt
thereof.
- 20 20. A compound according to claim 7 which is
5-[4-(4-(2-quinolinylmethyloxy)benzyloxy)phenyl]tetrazole or
a pharmaceutically acceptable salt thereof.
- 25 21. A compound according to claim 8 which is
5-[4-(4-(2-quinolinylmethyloxy)benzyloxy)benzyl]tetrazole or
a pharmaceutically acceptable salt thereof.
- 30 22. A compound according to claim 8 which is
5-[4-(3-(4-(2-quinolinylmethyloxy)benzyloxy)phenyl)-3-
methylbutyl]tetrazole or a pharmaceutically acceptable salt
thereof.
23. A compound according to claim 14 which is
5-[3-(3-(2-quinolinylmethyloxy)phenoxyethyl)phenyl]-
tetrazole or a pharmaceutically acceptable salt thereof.

24. A compound according to claim 14 which is
5-[2-(3-(2-quinolinylmethyloxy)phenoxy)methyl]phenyl]-
tetrazole or a pharmaceutically acceptable salt thereof.
- 5 25. A compound according to claim 14 which is
5-[4-(3-(2-quinolinylmethyloxy)phenoxy)methyl]phenyl]-
tetrazole or a pharmaceutically acceptable salt thereof.
26. A compound according to claim 14 which is
10 4-(3-(2-quinolinylmethyloxy)phenoxy)methyl]benzonitrile or a
pharmaceutically acceptable salt thereof.
27. A compound according to claim 14 which is
4-(3-(2-quinolinylmethyloxy)phenoxy)methyl]benzoic acid or a
15 pharmaceutically acceptable salt thereof.
28. A compound according to claim 14 which is
3-(3-(2-quinolinylmethyloxy)phenoxy)methyl]benzoic acid or a
pharmaceutically acceptable salt thereof.
- 20 29. A compound according to claim 15 which is
 α -(3-(4-(2-quinolinylmethyloxy)phenoxy)methyl)-
phenoxy)acetonitrile or a pharmaceutically acceptable salt
thereof.
- 25 30. A compound according to claim 15 which is
5-[3-(4-(2-quinolinylmethyloxy)phenoxy)methyl]-
phenoxy)methyl]tetrazole or a pharmaceutically acceptable salt
thereof.
- 30 31. A compound according to claim 15 which is
5-[4-(3-(2-quinolinylmethyloxy)phenoxy)methyl]-
phenoxy)methyl]tetrazole or a pharmaceutically acceptable salt
thereof.

32. A compound according to claim 15 which is 5-[3-(3-(2-quinolinylmethyloxy)phenoxy)methyl]-phenoxy-methyl]tetrazole or a pharmaceutically acceptable salt thereof.
- 5 33. A compound according to claim 15 which is 5-carboxy-2-(3-(2-quinolinylmethyloxy)phenoxy-methyl)phenoxyacetic acid or a pharmaceutically acceptable salt thereof.
- 10 34. A compound according to claim 15 which is 5-[2-(3-(2-quinolinylmethyloxy)phenoxy)methyl]tetrazole or a pharmaceutically acceptable salt thereof.
- 15 35. A compound according to claim 15 which is 5-[2-(3-(2-quinolinylmethyloxy)phenoxy)methyl]-5-carbomethoxyphenoxy-methyl]tetrazole or a pharmaceutically acceptable salt thereof.
- 20 36. A compound according to claim 7 which is 3-methoxy-4-(3-(2-quinolinylmethyloxy)benzyloxy)benzoic acid or a pharmaceutically acceptable salt thereof.
37. A compound according to claim 7 which is
25 methyl 3-methoxy-4-(3-(2-quinolinylmethyloxy)-benzyloxy)benzoate or a pharmaceutically acceptable salt thereof.
38. A compound according to claim 2 which is
30 5-[3-methoxy-4-(3-(2-quinolinylmethyloxy)phenoxy-methyl)phenyl]tetrazole or a pharmaceutically acceptable salt thereof.
39. A compound according to claim 2 which is
35 N-[3-methoxy-4-(3-(2-quinolinylmethyloxy)benzyloxy)-

benzoyl]benzenesulfonamide or a pharmaceutically acceptable salt thereof.

40. A compound according to claim 14 which is
5 3-methoxy-4-(3-(2-quinolinylmethyloxy)phenoxyethyl)-
benzoic acid or a pharmaceutically acceptable salt thereof.

41. A compound according to claim 1 which is
5-[2-(4-(2-quinolinylmethyloxy)phenoxyethyl)benzyl]tetrazole
10 or a pharmaceutically acceptable salt thereof.

42. A method for the treatment of hypersensitive ailments
in humans and mammals comprising administering thereto an
effective amount of a compound of the formula according to
15 claim 1.

43. A pharmaceutical composition wherein the active
ingredient is a compound according to claim 1 in admixture
with a pharmaceutical carrier.

INTERNATIONAL SEARCH REPORT

International Application No. **PCT/US88/03897**

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC(4): C07D 215/12; C07D 215/14; C07D 215/18; C07D 215/20; C07D 401/10; A61K 31/41; A61K 31/47; U.S.C1.: 546/168; 546/170; 546/171; See Attachment sheet 1.						
II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 25%; border-bottom: 1px solid black;">Classification System</th> <th style="border-bottom: 1px solid black;">Classification Symbols</th> </tr> <tr> <td style="border-right: 1px solid black; padding: 5px; vertical-align: top;">U.S.</td> <td style="padding: 5px;">546/16; 546/168; 546/170; 546/171; 546/172; 546/176; 546/180; 546/101; 514/311; 514/314</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸</div>			Classification System	Classification Symbols	U.S.	546/16; 546/168; 546/170; 546/171; 546/172; 546/176; 546/180; 546/101; 514/311; 514/314
Classification System	Classification Symbols					
U.S.	546/16; 546/168; 546/170; 546/171; 546/172; 546/176; 546/180; 546/101; 514/311; 514/314					
<div style="border: 1px solid black; width: 100%; height: 40px; margin: 0 auto;"></div> <p style="margin: 0;">CAS/ON LINE</p>						
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹						
Category [*]	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³				
A	U.S., A, 4,282,230 (HOEHN) published 04 August 1981. See entire document.	1-43				
A	U.S., A, 4,661,499 (YOUNG) published 28 April 1987. See entire document.	1-43				
P,Y	U.S., A, 4,769,461 (MUSSEY) published 06 September 1988. See entire document.	1-43				
Y	EP, A, 0,206,751 (YOUNG) published 30 December 1986.	1-43				
<div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p>[*] Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 48%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>						
IV. CERTIFICATION						
Date of the Actual Completion of the International Search 14 FEBRUARY 1989	Date of Mailing of this International Search Report <div style="text-align: center; font-size: 1.2em; font-weight: bold;">21 MAR 1989</div>					
International Searching Authority ISA/US	Signature of Authorized Officer <div style="text-align: center;"> DAVID SPRINGER </div>					

PCT/US88/03897
Attachment sheet 1

I. CLASSIFICATION OF SUBJECT MATTER (CONTINUED)

U.S.Cl.: 546/172; 546/176; 546/180; 546/16; 546/101;
514/311; 514/314

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